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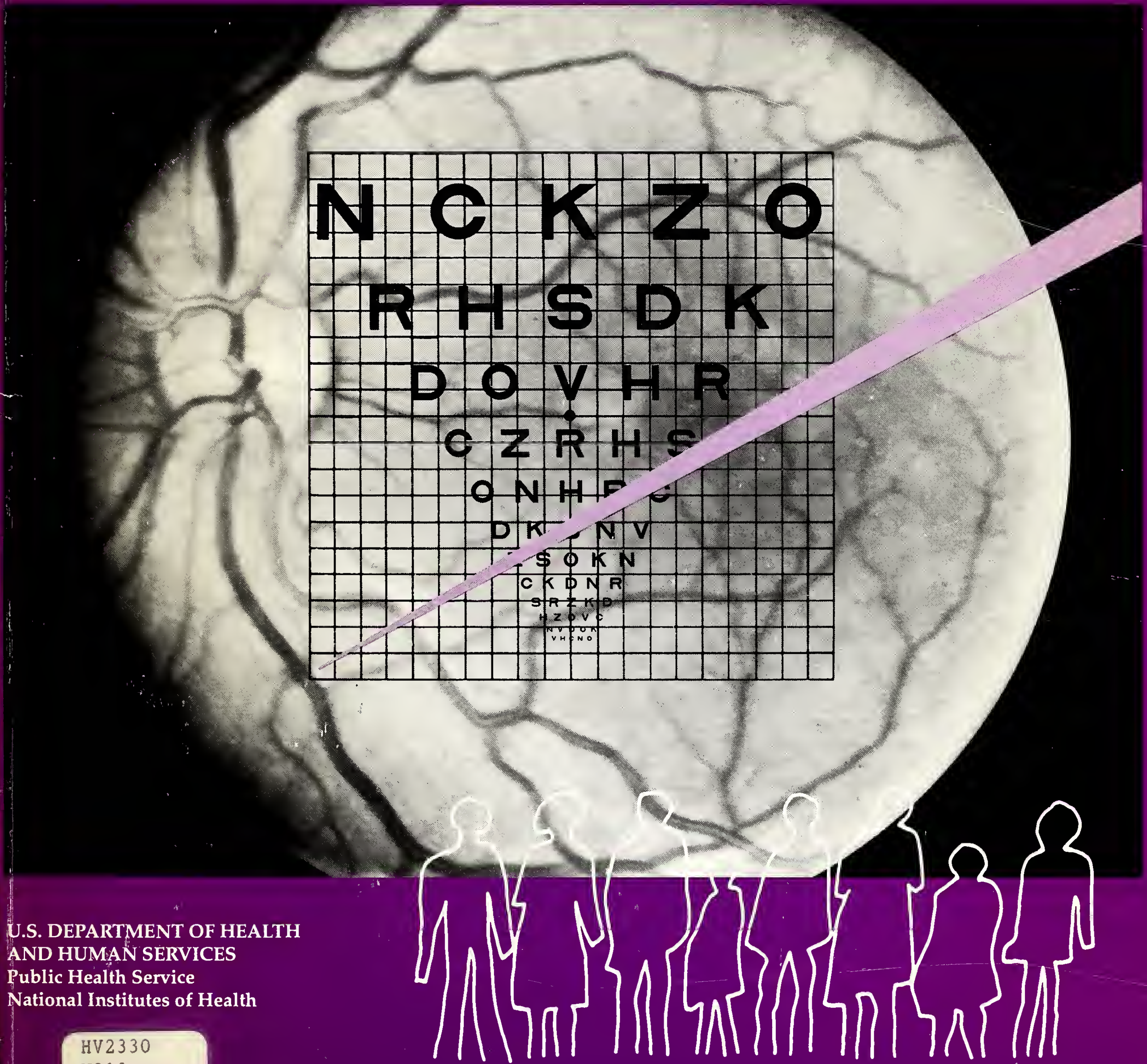
EVALUATING NEW APPROACHES TO THE TREATMENT OF EYE AND VISION DISORDERS



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Foreword

In 1989, four clinical trials supported by the National Eye Institute (NEI), the Fluorouracil Filtering Surgery Study, the Early Treatment Diabetic Retinopathy Study, the Sorbinil Retinopathy Trial, and the Prism Adaptation Study, reported new findings that are summarized in this booklet. These results fulfill the goal of all NEI-supported clinical research—to provide information that will help the practitioner treat his or her patients more effectively. Controlled clinical trials provide the best means to quantify and compare objectively the benefits and risks of new or alternative treatments for disease or injury, particularly when

- the difference between a new and old treatment is not clear,
- the disease naturally follows a chronic, variable, and erratic course, and
- a large number of factors, known or unknown, may influence both the course of the disease and the outcome of treatment.

Intended for the practitioner, this booklet describes 22 clinical trials currently supported by the NEI. Most of these trials depend heavily on the support of ophthalmologists and other eye care professionals in referring patients, encouraging their enrolled patients to remain in a trial for its duration, and participating in followup care. Such support can directly benefit the practitioner by hastening the study's attainment of results that can be incorporated into standard clinical practice.

Some of these clinical trials are actively seeking patient referrals and some have already published results or other information that is proving useful in daily practice. Some involve multiple cooperating centers, whereas others are being conducted within a single clinic. A few were initiated by the NEI, but most were developed by clinical investigators from the extramural community. Depending on the particular clinical questions being addressed and the nature of the therapy being evaluated, each of these studies incorporates the following elements of a well-designed and well-conducted clinical trial:

- high ethical standards—of paramount importance are patient welfare, informed consent, adherence to protocol, and careful data monitoring,
- concurrent control group(s), when possible,

- random assignment of patients to study and control groups when comparability of results among groups is essential,

- masking to minimize any bias of the examiner and, when possible, of the patient,

- adequate number of patients for results to be statistically and clinically significant,

- completeness of patient followup,

- use of biostatistical methods of data analysis, and

- continuous monitoring of adherence to protocol and of accumulating data.

To ensure objectivity, each study's data and safety monitoring committee is independent of the treating clinicians. The committee carefully reviews study data periodically to check for adverse or beneficial effects of treatment, any needed change to the protocol, and whether the study should be terminated because the question that it set out to investigate has been answered. The committee also guards against premature release of inconclusive findings.

It is important to remember that results from clinical trials provide evidence of treatment efficacy and risks in *groups* of patients; they do not necessarily predict the course that an individual patient will follow. Thus, the randomized, controlled clinical trial offers the practitioner objective and accurate information on the *likelihood* of improvement, risk of complications, or the *probability* of reaching a defined result. Armed with this information, the physician can practice the art of medicine in a scientific way.

In fiscal year 1990, the NEI provided approximately $29 million for the support of clinical trials. Among them are three new studies described in this booklet. One of these, the Studies of the Ocular Complications of AIDS (SOCA), incorporates an innovative treatment preference design for participants, and an adaptive administrative structure that may serve as a model for clinical trials in ophthalmology and other medical specialties. A number of clinical centers will participate in some or all SOCA components as they are developed.

Investigators who are considering applying to the NEI for support of clinical trials are encouraged to ask for information about planning grants, which are designed to support the development of clinical trial research plans. The planning grant provides a mechanism for early peer review of the rationale and the need for the trial as well as support for the development of a detailed Manual of Procedures.

The NEI Collaborative Clinical Vision Research Branch (CCVRB) is dedicated to the support and management of clinical and epidemiologic studies. Richard L. Mowery, Ph.D., Chief of the CCVRB, welcomes inquiries and suggestions about the trials described in this booklet, as do all of the clinical investigators listed. As new trials are begun or changes occur in the status of ongoing trials, the booklet will be revised and updated.

Carl Kupfer

CARL KUPFER, M.D.

Director
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Introduction

The trial descriptions in this booklet are arranged according to their relevance to the following five NEI disease-oriented programs, each of which encompasses a wide range of basic and applied research related to a number of eye and visual disorders:

- Retinal Diseases
- Corneal Diseases
- Cataract
- Glaucoma
- Strabismus, Amblyopia, and Visual Processing.

Information is provided on each trial's purpose and background, and its major design features are described. Also included are the study's patient eligibility criteria, patient recruitment and study status, summary of results to date, and bibliography, when available. In addition, the booklet provides the names of professional and institutional participants, the study chairman/co-chairmen, clinical centers, resource centers (e.g., coordinating centers and fundus photograph reading centers), data and safety monitoring committee members, and the NEI representative. A bibliography of articles resulting from four completed NEI-sponsored trials, and indices of investigators and institutions are listed at the end of this booklet.

Current Status of NEI-Supported Clinical Trials

September 1990

Trial	Patient Recruitment	Patient Followup	Results Published	Completed Trials
Retinal and Choroidal Diseases Program				
Age-Related Eye Disease Study (AREDS)	New Trial — Patient Recruitment Begins September 1991			
Branch Vein Occlusion Study (BVOS)			X	X
Central Vein Occlusion Study (CVOS)	X	X		
Collaborative Ocular Melanoma Study (COMS)	X	X		
Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)		X	X	
Diabetic Retinopathy Study (DRS)			X	X
Diabetic Retinopathy Vitrectomy Study (DRVS)			X	X
Early Treatment Diabetic Retinopathy Study (ETDRS)			X	X
Endophthalmitis Vitrectomy Study (EVS)	X			
Krypton-Argon Regression of Neovascularization Study (KARNS)		X		
Macular Photocoagulation Study (MPS)	X	X	X	
Randomized Trial of Beta-Carotene and Macular Degeneration		X		
The Silicone Study	X	X		
Sorbinil Retinopathy Trial (SRT)			X	X
Studies of the Ocular Complications of AIDS (SOCA)	New Trial — Patient Recruitment Began March 1990			
Corneal Diseases Program				
Berkeley Orthokeratology Study			X	X
Clinical Trial of Eye Prophylaxis in the Newborn	X	X		
Collaborative Corneal Transplantation Studies (CCTS)		X		
Herpetic Eye Disease Study (HEDS)	X			
Prospective Evaluation of Radial Keratotomy Study (PERK)		X	X	
Cataract Program				
Randomized Trial of Aspirin and Cataracts in U.S. Physicians		X		
Glaucoma Program				
Advanced Glaucoma Intervention Study (AGIS)	X	X		
Fluorouracil Filtering Surgery Study (FFSS)		X	X	
Glaucoma Laser Trial (GLT)		X		
Strabismus, Amblyopia, and Visual Processing Program				
Optic Neuritis Treatment Trial (ONTT)	X	X		
The Prism Adaptation Study (PAS)		X	X	

RETINAL AND CHOROIDAL DISEASES PROGRAM

Age-Related Eye Diseases Study (AREDS)

STUDY CHAIRMAN: Frederick L. Ferris III, M.D.

INSTITUTIONS: 11 Clinical Centers
2 Resource Centers

PURPOSE

To estimate the rates of development and progression, and to identify the associated risk factors, for age-related macular degeneration (AMD) and cataract.

BACKGROUND

AMD and cataract are the leading causes of visual impairment and blindness in the United States. The prevalence of both diseases increases dramatically after age 60. The Framingham Eye Study conducted from 1973 to 1975 found the overall prevalence of AMD to be 11.6 percent (8.1 percent for men and 15.1 percent for women). Framingham Eye Study data also documented that the prevalence of lens changes accompanied by visual acuity limitation increased from 4.5 percent for ages 52-64 to 45.9 percent for ages 75-85. The number of AMD cases in the aging U.S. population is expected to increase from 2.4 million in 1970 to 6.3 million in 2030.

Neither the etiology nor the natural history of AMD and cataract is known. Epidemiologic studies suggest that a number of risk factors may be associated with AMD and cararact but the strength of the evidence in support of these hypotheses varies. Possibly associated with AMD are personal characteristics such as age, race, height, family history, and strength of hand grip; ocular characteristics such as hyperopia and color of iris; and cardiovascular diseases, smoking, lung infections, and chemical exposures. Clinical and laboratory studies suggest the following factors may be associated with progression of AMD: drusen type, choroidal vascular diseases, and photic injury.

Epidemologic studies of cataract suggest that associated risk factors may include personal characteristics such as age, sex, race, occupation, and educational status; ocular characteristics such as iris color; diabetes mellitus, hypertension, drug exposure, smoking, and sunlight exposure. Animal studies and observational epidemiologic studies suggest that deficiencies in vitamins C and E, carotenoids, and the trace elements zinc and selenium also may be associated with the development of the two diseases, especially cataract. Although surgical treatment to remove cataract is very effective, cataract surgery carries risks as does any other surgery. Therefore, many research efforts focus on prevention or slowing cataract development as well as on determining the causes of cataract formation.

DESCRIPTION

The Age-Related Eye Diseases Study (AREDS) is a major research program to improve our understanding of the predisposing factors, clinical course, and prognostic factors of AMD and cataract.

PARTICIPANT ELIGIBILITY

Men and women between the ages of 60 and 75 years whose macular status ranges from no evidence of AMD in either eye to relatively severe disease with vision loss in one eye but good vision in the fellow eye, are eligible for the study, provided that their ocular media are clear enough to allow good fundus photography.

PARTICIPANT RECRUITMENT STATUS

Identification of potentially eligible study participants began on September 1, 1990. The detailed protocol will be developed by September 1, 1991, at which time enrollment and randomization of the 4,600 study participants will begin.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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Central Vein Occlusion Study (CVOS)

STUDY CHAIRMAN: John G. Clarkson, M.D.
INSTITUTIONS: 9 Clinical Centers
2 Resource Centers

PURPOSE

- To determine whether photocoagulation therapy can help prevent iris neovascularization in eyes with central vein occlusion (CVO) and evidence of ischemic retina.
- To assess whether grid-pattern photocoagulation therapy will reduce loss of central visual acuity due to macular edema secondary to CVO.
- To develop new data describing the course and prognosis for eyes with CVO.

BACKGROUND

Central vein occlusion is a common retinal vascular disorder with potentially blinding complications. The two major complications are reduced central vision caused by macular edema and neovascular glaucoma caused by iris neovascularization.

Other clinical trials have shown that laser photocoagulation is an effective treatment for complications found in diabetic retinopathy and branch vein occlusion, which have some features in common with CVO: Neovascularization and reduced visual acuity caused by macular edema occur in all three disorders. Evidence from small-scale studies suggests that a grid pattern of photocoagulation reduces macular edema in CVO patients, although the associated changes in visual acuity are variable. The CVOS is a detailed investigation of grid pattern photocoagulation in a larger randomized group of patients.

DESCRIPTION

Eligible patients will be divided into four groups:

Group N: Eyes with extensive retinal ischemia (at least 10 disc areas of nonperfusion) will be randomly assigned to receive panretinal photocoagulation or nontreatment.

Group M: Eyes with visual loss ascribable to macular edema will be randomly assigned to receive grid-pattern photocoagulation or nontreatment.

Group P: Eyes with relatively perfused retinas will be followed to provide information about the natural history of the disease.

Group I: Indeterminate eyes in which the retina cannot be visualized accurately because of hemorrhage will be followed in a natural history study.

Green argon laser with a slit lamp delivery system will be used for all treatments. Photographic documentation of retinal changes will be obtained at entry, post-treatment, and at specified followup visits for a period of at least 3 years. The frequency of followup visits will vary according to the group to which the CVO patient is assigned. Visual acuity, the primary outcome factor in the group with macular edema, will be measured according to a modified Early Treatment Diabetic Retinopathy Study protocol at each visit.

PATIENT ELIGIBILITY

Men and women must be age 21 or over and be willing to return for follow-up visits for 3 years following assignment into the appropriate group and randomization. Each of the four groups has specific eligibility criteria. Patients with retinal vascular disease other than that specified in the criteria, such as diabetic retinopathy, are ineligible. Patients with macular disease other than that due to CVO are ineligible for that portion of the study.

PATIENT RECRUITMENT

Ongoing. Recruitment began in August 1988.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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Collaborative Ocular Melanoma Study (COMS)

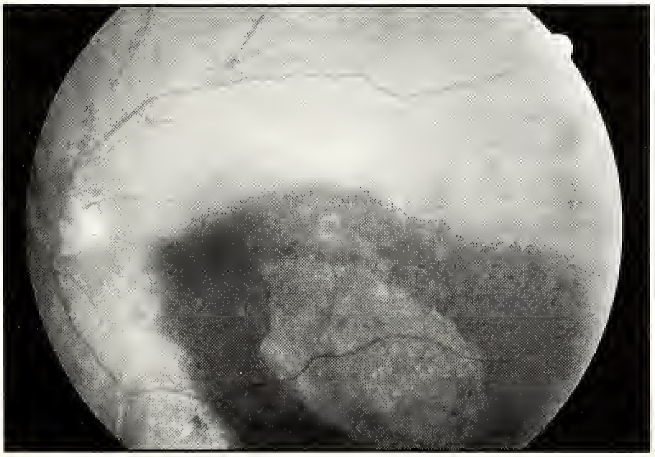
STUDY CHAIRMAN: Stuart L. Fine, M.D.
INSTITUTIONS: 32 Clinical Centers
5 Resource Centers

PURPOSE

- To evaluate therapeutic interventions for patients who have choroidal melanoma, the most common eye cancer affecting adults, and to assess the potential life-preserving as well as sight-preserving role of radiation therapy.
- To determine which of two standard treatments, removal of the eye or radiation therapy, is more likely to prolong survival of eligible patients with medium-sized choroidal melanoma.
- To determine whether preoperative radiation prolongs life for patients when eyes with large choroidal melanomas are enucleated.
- To design and conduct appropriate randomized trials for patients when eyes with choroidal melanomas are not eligible for either of the two current randomized trials.

BACKGROUND

For more than 100 years, removal of the eye (enucleation) has been the standard treatment for choroidal melanoma. During the past decade, interest has increased in radiation therapy because of the potential for saving the eye and perhaps some vision. However, the merits of radiation with respect to prolonging patient survival are unknown. The best data from non-randomized studies suggest that there is no difference in length of remaining life between patients treated with radiation and those whose eyes are enucleated. Thus, it is appropriate and necessary to conduct a randomized controlled clinical trial that will follow a large number of patients for many years in order to compare enucleation and radiation with respect to relative success in prolonging survival of choroidal melanoma patients.



Courtesy of Collaborative Ocular Melanoma Study Coordinating Center

A large choroidal melanoma in the posterior pole.

DESCRIPTION

The Collaborative Ocular Melanoma Study (COMS) is a set of long-term randomized controlled trials. In the trial for patients with tumors of medium size, enucleation and irradiation with an iodine-125 plaque will be compared on the basis of length of remaining life. All randomized patients will be followed for a minimum of 10 years, or until death. Prior to plaque irradiation, the margins of the tumor are located and the dimensions of the tumor are measured. A gold plaque/plastic disc insert assembly that contains the proper dosage and configuration of radioactive iodine seeds is sutured to the outside of the eye over the base of the tumor. This procedure makes possible the delivery of a high dose of radiation to a very localized area. The plaque is removed from the eye within approximately 3 to 5 days.

In the COMS trial of preoperative radiation, patients with large tumors are randomized to enucleation alone or to enucleation preceded by 20Gy of external beam irradiation. The two randomly assigned groups of patients also will be followed for 10 years or until death and compared on the basis of length of remaining life.

A non-randomized pilot study to assess management strategies for small tumors was halted in 1989.

The study is being conducted in 32 clinical centers located in major population areas of the United States and Canada. Each of these centers will be expected to enroll at least 12 eligible patients a year in the randomized trials. Five resource centers participate and have major roles in quality assurance for the Study. Approximately 2,000 patients with medium-sized tumors and 1,000 with large tumors will be enrolled. Information to be gathered and analyzed includes time to death from all causes, time to death from cancer (whether metastatic or not), diagnosis of other tumors, and complications of irradiation and changes in visual acuity.

PATIENT ELIGIBILITY

Men and women for the study must be age 21 or older and have primary choroidal melanoma in only one eye and no evidence of metastatic disease. Accurate estimation of tumor dimensions by echography must also be possible.

PATIENT RECRUITMENT

Ongoing. Recruitment began in November 1986.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

Fine SL: Do I take the eye out or leave it in? Arch Ophthalmol 104:653-654, 1986.

Earle J, Kline RW, Robertson DM: Selection of iodine 125 for the Collaborative Ocular Melanoma Study. Arch Ophthalmol 105:764-765, 1987.

Straatsma BR, Fine SL, Earle JD, et al: Enucleation versus plaque irradiation for choroidal melanoma. Ophthalmology 95:1000-1004, 1988.

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Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)

STUDY CHAIRMAN: Earl A. Palmer, M.D.

INSTITUTIONS: 23 Clinical Centers
4 Resource Centers

R
CRYO
P

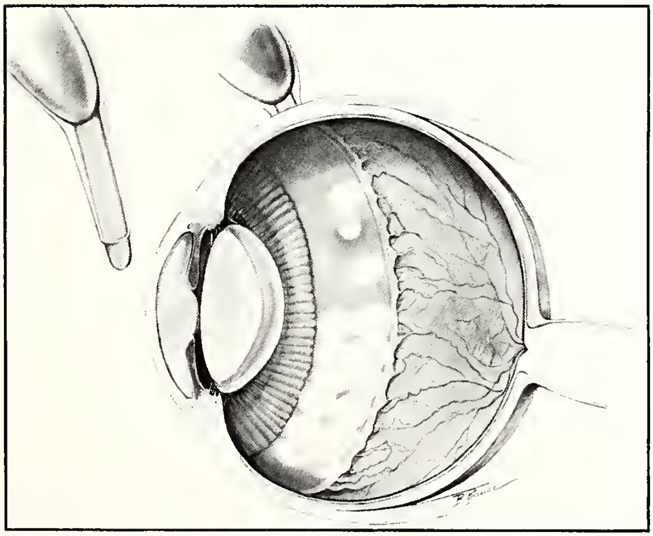
PURPOSE

- To determine the safety and efficacy of trans-scleral cryotherapy of the peripheral retina in certain low birth weight infants with retinopathy of prematurity (ROP) in reducing the number of infants who become blind from ROP.
- To study the natural history of retinal vascular development and ROP in very low birth weight infants.

BACKGROUND

Annually, in the United States alone, more than 500 infants are blinded by retinopathy of prematurity, a disease in which the retinal blood vessels increase in number and branch excessively, sometimes leading to hemorrhage or scarring. The number of babies affected is increasing as survival rates for smaller premature infants improve. The lower the birth weight, the higher the incidence of ROP.

Over 30 years ago, the National Institutes of Health sponsored a clinical trial which showed that if premature babies are given oxygen only as needed, the number of infants who develop ROP drops dramatically. Subsequently, hospitals cut back on giving excessive oxygen routinely to premature babies. But, with improvements in neonatal care over the last two decades, more premature infants with very low birth-weights are surviving, and the incidence of ROP has increased. In a recent NEI-supported study, very low birth weight infants' blood oxygen levels were monitored continuously by use of transcutaneous measurements as long as they needed oxygen therapy. The study showed that there is no statistically significant difference bewteen the rates of ROP in infants monitored on continuous oxygen theraphy and in those monitored only when they were receiving oxygen in excess of 40 percent. This and previous studies have led to the conclusion that factors other than oxygen must be involved in ROP.



Courtesy of The Johns Hopkins Medical Institutions

Artist's conception of how the interior of the eye might appear during cryotherapy. It shows the cryoprobe, the area of treatment (white spots), and the area yet to be treated.

DESCRIPTION

In some infants who develop ROP, the disease will spontaneously subside, permitting development of normal vision. But others who progress to a severe form of ROP will be in danger of becoming permanently blind. Although the cause of ROP is not fully explained, scientists have begun to look for ways in which ROP can be successfully treated, and to find the right time in the progression of the disease to use treatment. Cryotherapy, which destroys the edge of the retina through freezing, is one treatment that shows promise.

The multicenter trial of cryotherapy for ROP enrolled almost 5,000 premature infants who weighed no more than 1,250 grams at birth. These infants were at risk of developing ROP. While still in the intensive care nursery, infants enrolled in the study had their eyes examined at intervals. The pupils were dilated with eye drops, and the eyes were examined by an ophthalmologist using a binocular indirect ophthalmoscope to visualize the developing retina. The natural history of the condition of each infant's retinas was thereby recorded. When examination disclosed the severe form of ROP (threshold ROP) in both eyes, and the parents gave informed consent, one of the infant's eyes was randomly selected to receive cryotherapy. In this technique, a cryoprobe was used to freeze and thus destroy the outer edge of the retina, thereby arresting the development of the blood vessels growing wildly toward it.

Outcome of the therapy was assessed at 3 months and 12 months following randomization by means of an extensive examination that included fundus photography of both the treated and the control eyes, as well as measurement of visual function using preferential looking techniques. Such measurements allowed comparisons between fundus photographs and retinal function. The trained photograph readers who evaluated the pictures from both eyes were unaware of which eyes had received cryotherapy.

PATIENT ELIGIBILITY

Premature infants of either sex eligible for the natural history study had weighed less than 1,251 grams at birth, survived the first 28 days of life, and had no major ocular or systemic congenital anomalies. Infants who met these criteria and also had a threshold level of ROP (stage 3+ of the International Classification of Retinopathy of Prematurity defined as five or more contiguous or eight cumulative 30° sectors [clock hours] of stage 3 ROP in zone 1 or 2 in the presence of "plus" disease) could be referred for examination to determine eligibility for entry to the cryotherapy portion of the trial.

PATIENT RECRUITMENT STATUS

Recruitment began in January 1986 and was stopped January 22, 1988.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

The Cryotherapy for Retinopathy of Prematurity Cooperative Group reported preliminary results in 1988. This study of the safety and efficacy of cryotherapy in treating severe retinopathy of prematurity (ROP) registered 9,751 infants with birth weights less than 1251 grams at 23 study centers. Through a randomization protocol, 291 infants developed a defined threshold ROP. Cryotherapy was performed in half of the eyes. Twelve months after randomization, the results of masked grading of fundus photographs of the posterior pole indicated an unfavorable outcome in 25.7 percent of the eyes that had received cryotherapy and in 47.7 percent of the control eyes. Masked Teller Acuity Card assessment of grating acuity indicated an unfavorable functional outcome in 35 percent of the treated eyes, compared with 56.3 percent of the control eyes. These results indicate that cryotherapy reduces the risk of *unfavorable* retinal and functional outcome from threshold ROP.

Although the surgery was stressful, no major complications occurred during or following treatment. Physician diagnoses and the unbiased photograph gradings were statistically similar. These data support the efficacy of cryotherapy in reducing by approximately one-half the risk of unfavorable retinal outcome from threshold ROP.

There are, as yet, insufficient long-term data to permit a firm recommendation to apply cryotherapy routinely to both eyes of a patient with bilateral threshold ROP, to apply cryotherapy in any different pattern than that used in this trial, or to apply it to patients with less severe disease. The possible exception is that cryotherapy may be considered for both eyes whenever stage 3+ retinopathy of prematurity involves the posterior retina (zone 1) of both eyes.

All study patients, including those not randomized into the cryotherapy trial, were followed through their 12-month examinations. (More than 4,000 of these "natural history" infants were studied.) These Phase I data are currently being analyzed.

Long-term followup (Phase II) is under way. A selected cohort of patients is being examined annually to evaluate both retinal structure and visual function. This cohort includes all 257 surviving randomized patients and 1,192 "natural history" patients. The patients will be followed until they reach the age of 5 1/2 years. At the 5 1/2-year examination, a Snellen visual acuity test will be assessed for all study patients.

The followup information will allow physicians to answer three specific questions:

(1) Are there long-term structural or functional ocular sequelae in eyes treated with cryotherapy that would require reevaluation of the risk/benefit ratio of recommending cryotherapy?

(2) Do long-term data on structural and functional sequelae in untreated eyes with ROP indicate that the threshold for treatment should be reconsidered?

(3) Is the incidence of structural or functional ocular abnormalities any different in infants with mild ROP than in infants with no ROP?

PUBLICATIONS

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Early Treatment Diabetic Retinopathy Study (ETDRS)

STUDY CO-CHAIRMEN: Lloyd M. Aiello, M.D., and Frederick L. Ferris III, M.D.

INSTITUTIONS: 22 Clinical Centers
5 Resource Centers

PURPOSE

- To evaluate the effectiveness of both argon laser photocoagulation and aspirin therapy in delaying or preventing progression of early diabetic retinopathy to more severe stages of visual loss and blindness.
- To help determine the best time to initiate photocoagulation treatment in diabetic retinopathy.
- To monitor closely the effects of diabetes mellitus and of photocoagulation on visual function.
- To produce natural history data that can be used to identify risk factors and test etiologic hypotheses in diabetic retinopathy.

BACKGROUND

The ETDRS, which began in 1979, is a multicenter, randomized clinical trial designed to evaluate argon laser photocoagulation and aspirin treatment in the management of patients with nonproliferative or early proliferative diabetic retinopathy. Approximately 3,700 patients were recruited to be followed for a minimum of 4 years to provide long-term information on the risks and benefits of the treatments under study.

NEI photo

Argon laser treatment may now be considered for patients with diabetic macular edema.

DESCRIPTION

The eligibility criteria for the ETDRS were designed to include a broad range of macular edema severity, from a few small hard exudates within 1 disc diameter of the fovea with normal visual acuity to extensive cystoid spaces with a visual acuity of 20/200. Each study patient had one eye randomly assigned to immediate photocoagulation and the other eye to deferral of photocoagulation until high-risk proliferative retinopathy developed. During followup, additional photocoagulation was allowed for any degree of macular edema within the eligibility range but was required only for edema involving or threatening the center of the macula. The term "clinically significant macular edema" was coined to designate this level of severity.

The trial use of aspirin therapy was based on clinical observation and aspirin's possible mechanisms of action. Previous observations of diabetic patients who were taking large doses of aspirin for rheumatoid arthritis showed that the prevalence of retinopathy in this group was lower than what would be expected in the diabetic population at large. Evidence suggested that diabetics have altered platelet aggregation and disaggregation, which may contribute to the capillary closure seen in retinopathy. This abnormality is reversed by aspirin in vitro. However, because of aspirin's other possible mechanisms of action and its well-known side effects, such as allergic, idiosyncratic, and intolerance reactions, the use of this therapy in the ETDRS is being carefully controlled and monitored.

PATIENT ELIGIBILITY

Men and women between the ages of 18 and 70 years with moderate or severe nonproliferative diabetic retinopathy or mild proliferative retinopathy, with no previous photocoagulation treatment and visual acuity of 20/40 or better (20/200 or better if macular edema is present), were eligible for this study.

PATIENT RECRUITMENT

Recruitment began in December 1979 and was completed in July 1985. The 3,711 patients accepted for the study were followed through 1989.

CURRENT STATUS OF STUDY

Completed.

RESULTS

The first report from the ETDRS, published in 1985, dealt with the effectiveness of photocoagulation in the treatment of diabetic macular edema. It concluded that focal photocoagulation of clinically significant diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the patient's chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. The beneficial effects of photocoagulation treatment demonstrated in this trial suggest that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation.

The next three ETDRS reports specifically define clinically significant macular edema, describe treatable lesions in eyes with clinically significant macular edema, detail the treatment techniques used in the study, and provide clinical guidelines for the management of patients with diabetic macular edema.

In 1989 additional findings demonstrated that early photocoagulation, compared with deferral of photocoagulation, was associated with a small reduction in the incidence of severe visual loss (visual acuity less than 5/200 at two consecutive visits). Five-year rates were low in both the early treatment and deferral groups (2.6 percent and 3.7 percent, respectively). Provided careful followup can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage.

Aspirin treatment used in the ETDRS neither prevented the development of high-risk proliferative retinopathy nor increased the risk of vitreous hemorrhage. Aspirin treatment did not affect vision in any way. These results indicate no reason for people to avoid taking aspirin when it is needed for treatment of other medical problems.

PUBLICATIONS

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Endophthalmitis Vitrectomy Study (EVS)

STUDY CHAIRMAN:	Bernard H. Doft, M.D.
INSTITUTIONS:	15 Clinical Centers 2 Resource Centers

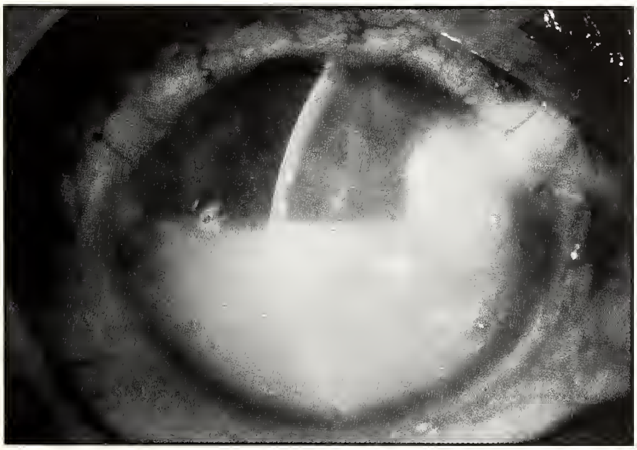
PURPOSE

- To determine the role of initial pars plana vitrectomy in the management of postoperative bacterial endophthalmitis.
- To determine the role of intravenous antibiotics in the management of bacterial endophthalmitis.
- To determine which factors, other than treatment, are predictors of outcome in postoperative bacterial endophthalmitis.

BACKGROUND

Endophthalmitis is a serious ocular infection that can result in blindness. Approximately 70 percent of cases occur as a direct complication of intraocular surgery. Current management requires culture of intraocular contents and intravitreal antibiotic administration. Vitrectomy surgery may be beneficial in the management of endophthalmitis by removing infecting organisms and their toxins and has been shown to be of value in various animal models of endopthalmitis. However, human studies have not shown an advantage to vitrectomy with intraocular antibiotics compared to intraocular antibiotics alone.

In all large comparison studies to date, eyes with the worst initial presentations were those selected for vitrectomy. Because of the selection bias involved in determining which cases received vitrectomy, existing clinical information on the efficacy of the procedure for treating endophthalmitis is inconclusive. Determining the role of initial vitrectomy and whether certain subgroups of patients may benefit, will help the clinician in the management of endophthalmitis.



Courtesy of Endophthalmitis Vitrectomy Study

Hypopyon in post-cataract extraction endophalmitis.

In addition, although systemic antibiotics historically have been used in the management of endophthalmitis, there has been little evidence to support their efficacy, but many reports of toxic systemic effects. In view of this, the role of systemic antibiotics will be assessed in the management of endophthalmitis.

DESCRIPTION

Endophthalmitis Vitrectomy Study (EVS) patients are randomized to one of two standard treatment strategies for the management of bacterial endophthalmitis. Eyes receive either (1) initial pars plana vitrectomy with intravitreal antibiotics, followed by retap and reinjection at 36-60 hours for eyes doing poorly as defined in the study, or (2) initial anterior chamber and vitreous tap/biopsy with injection of intravitreal antibiotics, followed by vitrectomy and reinjection at 36-60 hours in eyes doing poorly. In addition, all eyes are randomized to either treatment or no treatment with intravenous antibiotics.

Study end points are visual acuity and clarity of ocular media, the latter assessed both clinically and photographically. Each patient's initial end point assessment occurs at 3 months, after which procedures to improve vision, such as late vitrectomy for nonclearing ocular media, may be performed. The final outcome assessment occurs at 9 months. Multiple centers are cooperating by enrolling 420 eyes during a proposed 42-month recruitment period.

PATIENT ELIGIBILITY

Men and women are eligible for entry into the EVS if they have clinical signs and symptoms of bacterial endophthalmitis in an eye that has had cataract surgery or lens implantation within 6 weeks of onset of infection. The involved eye must have either hypopyon or enough clouding of anterior chamber or vitreous media to obscure clear visualization of second-order arterioles, a cornea and anterior chamber in the involved eye clear enough to visualize some part of the iris, and a cornea clear enough to allow the possibility of pars plana vitrectomy. The eyes should also have a visual acuity of 20/50 or worse and light perception or better.

Patients are ineligible when the involved eye is known at the time of study entry to have had any preexisting eye disease that limited best-corrected visual acuity to 20/100 or worse prior to development of cataract, any intraocular surgery prior to presentation, (except for cataract extraction or lens implantation), treatment for endophthalmitis prior to presenting at the study center, or any ocular or systemic condition preventing randomization to any of the study groups.

PATIENT RECRUITMENT STATUS

Recruitment began in February 1990.

CURRENT STATUS OF THE STUDY

Ongoing.

RESULTS

None.

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Krypton-Argon Regression of Neovascularization Study (KARNS)

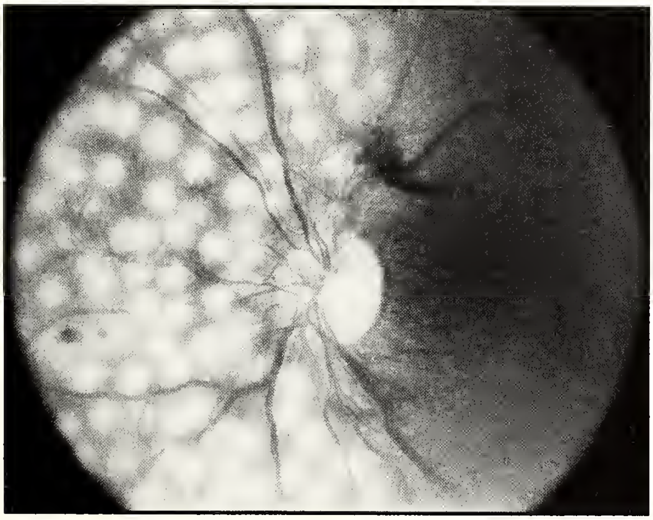
STUDY CO-CHAIRMEN:	Frederick L. Ferris III, M.D., and Lawrence J. Singerman, M.D.
INSTITUTIONS:	32 Clinical Centers 2 Resource Centers

PURPOSE

- To evaluate whether krypton laser treatment is as effective at causing regression of diabetic disc neovascularization as treatment with the argon laser when they are both used with identical panretinal photocoagulation patterns.
- To assess the vision of study patients.
- To test the feasibility of a prototype NEI-sponsored multicenter clinical trial in which participating clinics are not financially reimbursed, and both the Coordinating and Fundus Photograph Reading Center functions are carried out by staff of the NEI Biometry and Epidemiology Program.

BACKGROUND

The Krypton-Argon Regression of Neovascularization Study (KARNS) is a randomized clinical trial designed to compare the effectiveness of argon and krypton laser photocoagulation in causing the regression of preexisting neovascularization on the disc in diabetic retinopathy. The main theoretical advantage for the krypton laser in the treatment of diabetic retinopathy is that the red laser beam penetrates blood and may be more effective in making burns in the pigment epithelium in eyes with vitreous hemorrhage.



Courtesy of Harry Flynn, University of Miami School of Medicine

Neovascularization of the optic nerve and argon laser photocoagulation.

The burns produced by the krypton laser in the retina are different from those produced by the argon laser. Specifically, the burns from the krypton laser do not involve the inner retina. Also, in using the krypton laser the nerve fiber layer near the macula is spared. In contrast, nerve fiber layer burns are common with the argon laser. Pigment epithelium and outer segments are usually destroyed by both krypton and argon photocoagulation, but there is no uptake of energy by the vascular tissues within the retina when krypton photocoagulation is used. Further, krypton treatment is more effective in penetrating brunescent nuclear sclerosis of the lens and can be used to treat some diabetic eyes with this condition that are untreatable with the argon laser.

DESCRIPTION

The recruitment goal of this study was 1,000 patients, each followed for 1 year. Each patient has an eye randomized to either krypton panretinal photocoagulation or argon panretinal photocoagulation. But, if the other eye becomes eligible, it can be randomized to the study at the discretion of the treating ophthalmologist. In this situation, both eyes could be assigned to the same treatment. For patients with two eligible eyes, one eye is treated with krypton and the other with argon panretinal photocoagulation. In this situation, the right eye is randomly assigned to either argon or krypton and the left eye receives the alternate treatment. Fundus photographs are taken of the disc and macula prior to treatment and during the 3-month and 1-year followup visits.

The pilot study of KARNS affirms the benefits of argon laser photocoagulation in the treatment of proliferative diabetic retinopathy, as demonstrated in the NEI-supported Diabetic Retinopathy Study conducted a decade ago (see publication list). The KARNS study will help to determine whether use of the krypton laser can be as effective as the argon laser in causing regression of diabetic neovascularization, but with fewer side effects such as smaller loss of central visual acuity.

PATIENT ELIGIBILITY

Eligible are men and women between the ages of 18 and 80. They have neovascularization on the optic nerve head (NVD) that is considered greater than, or equal to, DRS Standard Photograph 10A in the opinion of the examining ophthalmologist. NVD is defined as new vessels on the surface of the retina or further forward in the vitreous cavity over the disc or within 1 disc diameter of the disc in any direction.

Patients must have ocular media of sufficient clarity that fundus photographs can be taken to allow the extent of neovascularization on the optic nerve head to be assessed. (If vitreous hemorrhage or other media opacity prevents adequate visualization of the neovascularization, it will greatly impair the ability to assess the effect of photocoagulation.) Another requirement for patient eligibility is the presence of an area of at least three quadrants of retina in which full argon or krypton laser panretinal photocoagulation can be placed (i.e., vitreous hemorrhage and/or traction retinal detachment that interferes with treatment should be less than one quadrant in extent).

PATIENT RECRUITMENT

Recruitment began in January 1984 and was completed in May 1990.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

Singerman LJ, Ferris FL, Passloff RW: Red krypton laser (RKL) versus blue-green argon laser (BGAL) treatment of proliferative diabetic retinopathy (PDR) with neovascularization of the disc (NVD). Invest Ophthalmol Vis Sci 24(Suppl):172, 1983.

Ferris FL, Singerman LJ: Inexpensive collaborative research. Invest Ophthalmol Vis Sci 24(Suppl):171, 1983.

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Macular Photocoagulation Study (MPS)

STUDY CHAIRMAN: Stuart L. Fine, M.D.

INSTITUTIONS: 15 Clinical Centers
2 Resource Centers

Macular
Photocoagulation
Study

PURPOSE

To evaluate laser treatment of neovascular maculopathy through randomized, controlled clinical trials. The Macular Photocoagulation Study (MPS) currently consists of three sets of randomized controlled clinical trials. Change in best-corrected visual acuity from baseline is the primary outcome for all MPS trials. Other measures of vision are evaluated in each set of trials. The purpose of each is described below.

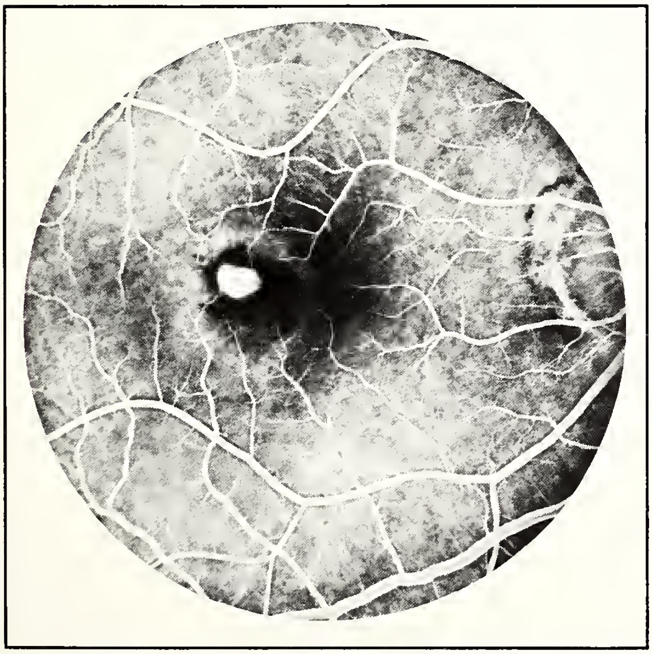
Argon Study: To determine whether argon blue-green laser photocoagulation of leaking abnormal blood vessels in choroidal neovascular membranes outside the fovea (200 to 2,500 microns from the center of the foveal avascular zone [FAZ]) is of benefit in preventing or delaying loss of central vision in patients with age-related (senile) macular degeneration (AMD), presumed ocular histoplasmosis (POH), and idiopathic neovascular membranes (INVM). A separate trial is being conducted for each of the three underlying conditions.

Krypton Study: To determine whether krypton red laser photocoagulation of choroidal neovascular lesions within 1 to 199 microns of the center of the FAZ is of benefit in preventing or delaying large losses of visual acuity in patients with AMD, POH, and INVM. A separate trial is being conducted for each of the three underlying conditions.

Foveal Study: To determine whether laser photocoagulation is of benefit in preventing or delaying further visual acuity loss in patients with new (never treated) or recurrent (previously treated) choroidal neovascularization under the fovea. Two separate trials, one for each type of lesion, are under way.

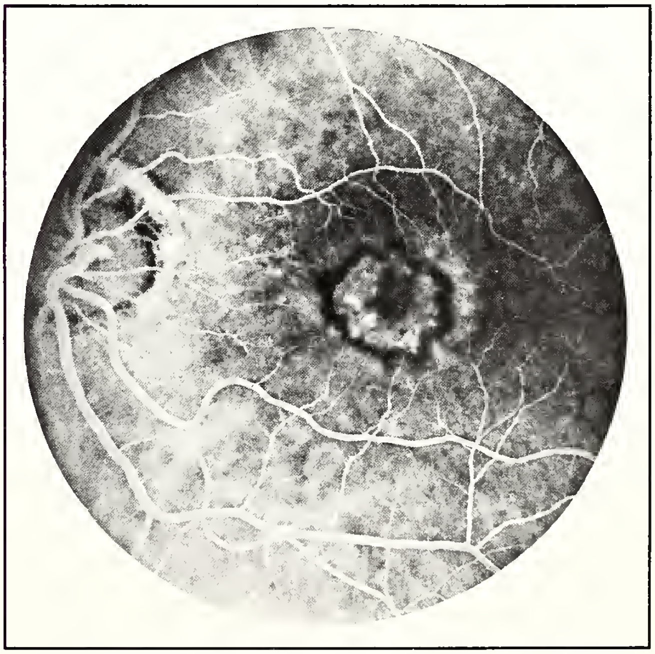
BACKGROUND

Age-related macular degeneration is the leading cause of severe visual acuity loss in the United States among people over age 60. Presumed ocular histoplasmosis is a leading cause of visual loss in young and middle-aged persons living in the histo belt, an area that includes all of Arkansas, Kentucky, Missouri, Tennessee and West Virginia, and major portions of Alabama, Illinois, Indiana, Iowa, Kansas, Louisiana, Maryland, Mississippi, Nebraska, Ohio, Oklahoma, Texas and Virginia. Both disorders are associated with the formation of choroidal neovascular membranes that damage



Courtesy of Macular Photocoagulation Study Reading Center

Juxtafoveal neovascular membrane.



Courtesy of Macular Photocoagulation Study Reading Center

Subfoveal neovascular membrane.

the macula. Idiopathic choroidal neovascularization leads to acute loss of central vision but is not attributed to any known disease process. In all three disorders visual loss results from complications of choroidal neovascularization in the macula.

DESCRIPTION

The first set of MPS randomized trials, the Argon Study, focused on the effectiveness of photocoagulation with argon blue-green laser in eyes with discrete extrafoveal neovascular membranes. The study investigators began recruiting patients in 1979. It was estimated that 550 patients with AMD and 750 with POH would be required. Followup was to continue for 5 years to determine whether argon laser photocoagulation treatment could prevent or delay visual acuity loss in these patients.

After the initiation of the Argon Study, a new krypton red laser became available. The new wavelength offered theoretical advantages over the argon laser for treating neovascular membranes inside the FAZ of the macula. Availability of the new laser led to an expansion of the MPS. The Krypton Study design was analogous to the Argon Study, with the investigation of three underlying conditions, except that lesions were closer to the fovea.

The third set of MPS clinical trials, the Foveal Study, was designed to determine whether laser photocoagulation is effective for delaying or preventing further visual acuity loss in AMD patients who have subfoveal new vessels. The study will provide information comparing argon green with krypton red laser treatment of these lesions. About 350 patients will be required for each part of the Foveal Study.

PATIENT ELIGIBILITY

Common Eligibility Criteria for the Argon, Krypton and Foveal Studies: All men and women must be experiencing visual symptoms attributable to the macular lesion, such as decreased visual acuity or Amsler grid distortion, at the time of entry into the study and must have visible hyperfluorescence characteristic of choroidal neovascularization on fluorescein angiography. AMD patients must be 50 years of age or older and have drusen visible in the macula of at least one eye. POH patients must be at least 18 years old and must have at least one atrophic histo spot in one or both eyes. INVM patients must be at least 18 years old and have no evidence of AMD, POH, angioid streaks, high myopia, diabetic retinopathy, or any other condition that could be presumed to be the cause of the neovascular membrane.

In particular, the patient must have neither drusen greater than MPS Standard Photograph No. 1.1 nor histo spots in either eye.

Additional Patient Eligibility Criteria for the Argon Study: Each man or woman should have a visible serous detachment of the sensory retina with a diffuse area of leakage, a choroidal neovascular membrane outside the fovea (200-2,500 microns from the center of the FAZ), and visual acuity of 20/200 or better in the study eye.

Additional Patient Eligibility Criteria for the Krypton Study: All men and women must have a neovascular lesions consisting of neovascularization, and possibly blood and/or pigment, that extends as close as 1 to 99 microns from the center of the FAZ. Visual acuity of the study eye must be 20/400 or better.

Additional Patient Eligibility Criteria for the Foveal Study: Only AMD men and women currently are eligible for this study. Fluorescein angiography of each must show evidence of a leaking choroidal neovascular membrane, some part of which extends under the center of the FAZ, or a neovascular lesion consisting of an old treatment scar and contiguous leaking neovascularization within 150 microns of the center of the FAZ. New, never-treated subfoveal lesions must be less than 4 disc areas in size. Recurrent lesions must be less than 6 disc areas in size, including the old treatment and new neovascularization. Best-corrected visual acuity may be no better than 20/40 and no worse than 20/320.

PATIENT RECRUITMENT

Recruitment for the MPS, which began in February 1979, was completed in the Argon Study in 1983 and Krypton Study in 1987. Recruitment is ongoing in the Foveal Study.

CURRENT STATUS OF STUDY

Foveal Study: Ongoing. Argon Study: Analysis and reporting.

RESULTS

Recruitment of AMD patients in the Argon Study was halted in March 1982 and of POH and INVM patients in May 1983 after 236 patients with AMD, 265 with POH, and 67 with INVM had been enrolled. These decisions were based on findings that argon laser treatment, as applied in the study, can dramatically reduce severe visual acuity loss in these conditions. Patients in the Argon Study trials were discharged from the study as they completed 5 years of regular followup examinations.

In the Krypton Study, patient recruitment was halted for the POH trial in December 1986 because of evidence of treatment benefit in these patients. Recruitment of patients with age-related macular degeneration and idiopathic membranes was halted in December 1987. In 1989, sufficient data had accumulated to demonstrate that there was a small overall beneficial effect of krypton red laser treatment in eyes with AMD. The benefit was most pronounced in normotensive patients and disappeared among hypertensive patients. Findings for patients with INVM were intermediate between those of patients with AMD and POH. Patients in the Krypton Study have been discharged as they completed 5 years of regular followup. All remaining patients will be discharged from the study by March 31, 1991.

In December 1989, patient enrollment was completed in the Foveal Study trial for never-treated subfoveal choroidal neovascularization; 373 patients were randomized. Enrollment of patients with subfoveal recurrence after laser treatment continues.

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Randomized Trial of Beta-Carotene and Macular Degeneration

STUDY CHAIRMAN: Charles H. Hennekens, M.D., Dr.P.H.
INSTITUTION: Brigham and Women's Hospital, Inc.
2 Resource Centers

PURPOSE

- To determine whether 50 mg of beta-carotene taken every other day reduces the risk of developing age-related macular degeneration (AMD) among male U.S. physicians who were ages 40 to 84 in 1982.
- To investigate the possible relationship of AMD with other antioxidants, including vitamins A, C, E, and selenium.
- To identify potential risk factors for development of AMD. Possible risk factors include height, systemic hypertension, cardiovascular disease, blood cholesterol, cigarette smoking, iris and skin color, sunlight exposure, body mass index, diabetes, and alcohol intake.

BACKGROUND

Macular degeneration is a major cause of blindness in the United States. It is the leading cause of new cases of blindness in people age 65 and older. The National Eye Institute estimates that each year an additional 165,000 people, mainly in the older age groups, develop macular disease. Among all people with macular degeneration, approximately 116,000 are affected by the neovascular form of the disease. Although laser treatment has been demonstrated to be an effective treatment for patients with certain forms of neovascular membranes, or exudative AMD, for most patients there is no available treatment.

The pathogenesis of AMD is only partly understood, and its etiology remains obscure. The Retinal and Choroidal Diseases Panel of the National Advisory Eye Council has stated that "none of the fundamental causes of any type of macular disease is known, and none can be prevented." Thus, this panel recommended that one of the NEI's program development priorities should be to "initiate epidemiologic studies of macular diseases to identify possible causative, protective, or aggravating factors."

DESCRIPTION

This trial is part of the Physicians' Health Study sponsored by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health, with funding for eye epidemiologic data evaluations provided by the NEI. It is an ongoing, randomized, placebo-controlled trial of aspirin in the prevention of cardiovascular mortality and beta-carotene in the prevention of cancer. Following randomization, each of the 22,071 physicians enrolled was assigned to one of four groups to take either aspirin or its placebo and beta-carotene or its placebo. Follow-up questionnaires are sent at 6 and 12 months after randomization and every 12 months thereafter. The average length of followup is more than 5 years.

The hypothesis that beta-carotene levels are inversely related to AMD is supported by experimental studies on the relationship between antioxidants and retinal morphology and function. There is increasing evidence that visible and ultraviolet light can damage the retina through production of superoxide radicals. Antioxidants, including beta-carotene, vitamins A, E, and C, and selenium, protect against oxidative damage by acting as scavengers for the superoxide radicals.

Epidemiologic data from the first National Health and Nutrition Examination Survey (NHANES-I) is also consistent with a link between antioxidants and AMD; the frequency of consumption of fruits and vegetables rich in vitamin A (beta-carotene) was negatively correlated with AMD after adjustment for demographic and medical factors.

Data from this study will determine whether one 50-mg-beta-carotene capsule taken on alternate days protects against the development of AMD and whether additional risk factors emerge after simultaneously controlling for other potential confounding factors.

Reported diagnoses of AMD are confirmed by medical record review. A validation study on a subsample of physicians will be conducted to investigate the relationship between self-reported ophthalmic data and medical record review with that obtained from direct examination. The primary analysis will be a comparison of incidence of reported AMD in the beta-carotene and placebo groups. The Cox proportional hazards model will also be used to determine whether there is a difference in time to diagnosis of AMD between the two groups.

PATIENT ELIGIBILITY

When the Physicians' Health Study was established in the early 1980's by the NHLBI to collect data on a stable population at risk for heart attack, only male physicians were studied because they were thought to be at higher risk than females for ischemic heart problems. The study population consists of 22,071 male U.S. physicians, ages 40 to 84 in 1982, with no history of myocardial infarction, cancer, kidney disease, renal disease, or any other contraindication to the use of aspirin or beta-carotene, including regular use of corticosteroids.

PATIENT RECRUITMENT

Recruitment for the Physicians' Health Study began in April 1982 and was completed in December 1984. The Randomized Trial of Beta-Carotene and Macular Degeneration began evaluating data from that study in 1990.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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The Silicone Study

STUDY CHAIRMAN: Stephen J. Ryan, M.D.
INSTITUTIONS: 13 Clinical Centers
2 Resource Centers

Silicone Study

PURPOSE

- To compare, through a randomized, multicenter surgical trial, the postoperative tamponade effectiveness of intraocular silicone oil with that of an intraocular long-acting gas [perfluoropropane (C_3F_8)] for the management of retinal detachment complicated by proliferative vitreoretinopathy (PVR) using vitrectomy and associated techniques.
- To evaluate the ocular complications that result from the use of silicone oil and gas.

BACKGROUND

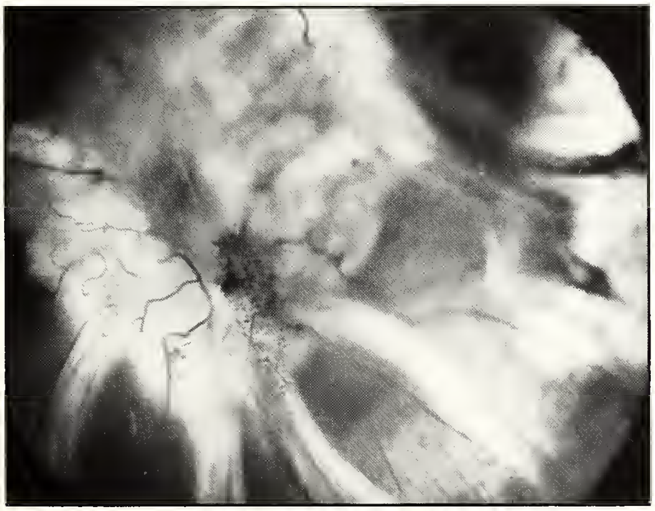
The treatment of retinal detachment complicated by PVR remains controversial. Although some cases are managed successfully by pars plana vitrectomy and with temporary tamponade provided by intraocular gas, others eventually redetach with this technique. Preliminary reports indicate that prolonged tamponade with liquid silicone results in improved anatomical success but the eventual visual outcome may be prejudiced by silicone-related complications, particularly glaucoma and keratopathy. The addition to vitrectomy surgery of hydraulic reattachment by simultaneous fluid/gas exchange has proved to be an important development. Although complications are few with these procedures, subsequent redetachment is frequent.

DESCRIPTION

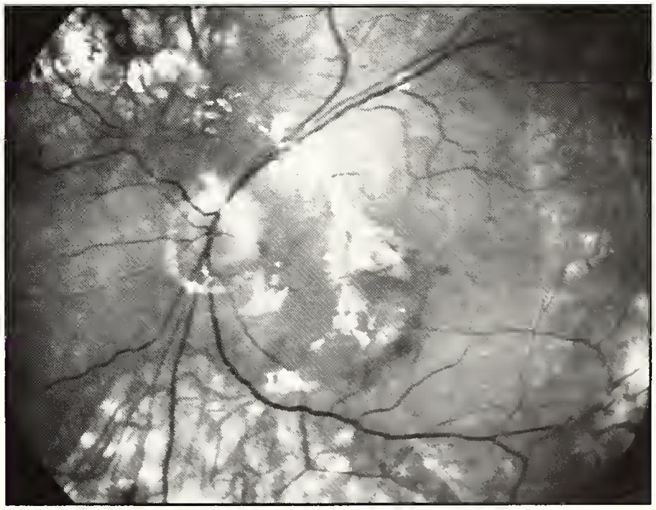
The Silicone Study is a randomized trial to investigate the relative merits of silicone oil or gas as tamponade modalities. All Study patients undergo vitrectromy and are randomized intraoperatively to either silicone oil or gas. Two groups of eyes are entered into the study: eyes that have not had a prior vitrectomy (Group 1) and those that have undergone previous vitrectomy outside the study (Group 2).

A critical element in the study is a standardized surgical procedure for PVR. This surgical procedure, intended to relieve retinal traction by utilizing vitrectomy techniques, is followed by assessment of the relief provided by an intraocular air tamponade. The eye is randomized to silicone oil or gas only after completion of the entire surgical procedure in order to eliminate investigator bias that might develop through knowledge of the treatment modality.

Patients are examined 5 to 14 days following the randomization and again at 1, 3, 6, 12, 18, 24 and 36 months after that date. Repeated surgery is permitted for either treatment modality. The Fundus Photograph Reading Center staff process and analyze photographs


Courtesy of The Silicone Study Reading Center

Ocular fundus view shows extensive scar tissue obscuring optic nerve and macula. Retina is totally detached.


Courtesy of The Silicone Study Reading Center

The same view 14 months later, following successful surgery to remove scar tissue and reattach retina by placement of silicone oil.

taken at all of the clinics, grade the preoperative severity of PVR on the basis of baseline visit photographs, and confirm the macular status at followup visits.

End points of the study are visual acuity of 5/200 or greater and macular reattachment for 6 months following the final surgical procedure. The successful outcomes and complication rates of the two modalities will be compared. A total of 368 adult patients will be enrolled, 176 in Group 1 and 192 in Group 2.

PATIENT ELIGIBILITY

Eligibility criteria include, but are not limited to, PVR of Grade C-3 or greater, according to the Retina Society Classification, and visual acuity of light perception or better.

PATIENT RECRUITMENT

Ongoing. Recruitment began in September 1985.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

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Sorbinil Retinopathy Trial (SRT)

STUDY CHAIRMAN:	Matthew D. Davis, M.D.
FUNDING AND COORDINATION:	Michael Peterson, Ph.D., Pfizer Inc.
INSTITUTIONS:	11 Clinical Centers 2 Resource Centers

PURPOSE

To evaluate the safety and efficacy of the investigational drug, sorbinil, an aldose reductase inhibitor, in preventing the development of diabetic retinopathy and neuropathy in persons with insulin-dependent diabetes.

The Sorbinil Retinopathy Trial (SRT) is a unique collaboration between private industry and the Federal Government in designing, funding, and conducting a multicenter, randomized clinical trial. Pfizer Inc. is supporting 10 of the 11 participating clinical centers, providing the medication, and funding the Data Coordinating Center and Fundus Photograph Reading Center. The National Eye Institute is providing funding for the Policy, Data, and Safety Monitoring Committee and for its own participating clinical center.

BACKGROUND

During the last two decades, vision researchers have studied intensively the role of the enzyme aldose reductase (AR) in diabetic cataract and in other diabetic complications. The potentially damaging effects of AR in diabetes were first discovered in the lens fiber cells where the enzyme catalyzes the reduction of high levels of glucose to sorbitol through the polyol pathway and initiates a sequence of events that eventually results in opacification of the lens. Because sorbitol, a sugar alcohol, and a subsequent product of glucose metabolism, fructose, cannot readily diffuse across cell membranes, they become trapped in lens fiber cells. There they accumulate at unusually high levels and exert a significant osmotic stress, causing an influx of water and swelling of the lens fibers. Major electrolytic and osmotic changes then occur, leading to lens opacity.

More recently, the detection of AR in the pericytes of retinal capillaries, cells that are involved very early in the evolution of diabetic retinopathy, suggests that this enzyme may also play a role in the pathogenesis of this disorder. Scientists now know that AR is present in nerve tissue, and they speculate that in diabetes it induces the depletion of myoinositol, which leads to the lessening of nerve conduction velocity in diabetic neuropathy.

Chemicals that inhibit aldose reductase have proved effective in preventing damage to the lens, in preventing thickening of retinal capillary basement membranes in diabetic animals, and in improving nerve conduction velocity values in patients with diabetic neuropathy. Therefore, it is possible that AR inhibitors also may be able to prevent, delay, or halt the development or progression of diabetic retinopathy.

DESCRIPTION

To test this hypothesis, an AR inhibitor developed by Pfizer Inc., sorbinil, is being studied in this clinical trial. (Other AR inhibitors are undergoing study in clinical trials sponsored by Ayerst and Alcon.) Patients in the SRT were randomly selected to receive either one tablet of sorbinil or a placebo once a day for about 3 years. Changes in retinopathy and neuropathy from baseline were evaluated every 9 months, and comparisons are now being made between treatment groups. Followup was completed in June 1988, and data are being analyzed. Five hundred patients participated in the study.

PATIENT ELIGIBILITY

Men and women eligible for the SRT had had diabetes for 1 to 15 years and were between ages 18 and 56 at the time of enrollment. They had begun taking insulin before their 41st birthday. Their hemoglobin A1c value was within the diabetic range. On retinal examination, they showed no evidence of, or only very mild, retinopathy, with no more than five microaneurysms per eye. Women were postmenopausal, sterile, or had an IUD in place.

PATIENT RECRUITMENT

Recruitment began in August 1983 and was completed in May 1986.

CURRENT STATUS OF STUDY

Completed.

RESULTS

The Sorbinil Retinopathy Trial Research Group reported results in 1990. This study evaluated the safety and efficacy of the investigational drug, sorbinil, an aldose reductose inhibitor, in preventing the development of diabetic retinopathy and neuropathy in persons with insulin-dependent diabetes at 11 clinical centers.

A total of 497 patients ages 18 to 56 years with insulin-dependent diabetes mellitus for 1 to 15 years were randomly assigned to take oral sorbinil or a placebo and followed up for a median of 41 months. The percentage of patients whose retinopathy severity grade at maximum followup had worsened by two or more levels was not significantly different between the two treatment groups (28% in the sorbinil group and 32% in the placebo group, P=.344). The number of microaneurysms increased at a slightly slower rate in the sorbinil group than in the placebo group, with statistically significant differences at 21 (P=.046) and 30 (P=.039) months but not at the maximum followup (P=.156). About 7% of the patients assigned sorbinil developed a hypersensitivity reaction in the first 3 months.

On the basis of these results, it is unlikely that sorbinil administered at a dosage of 250 mg daily for 3 years has a clinically important effect on the course of retinopathy in adults with insulin-dependent diabetes of moderate duration. Our data are consistent, however, with a slightly slower progression rate in the microaneurysm count among patients assigned to take sorbinil, a finding of uncertain clinical importance.

PUBLICATIONS

The Sorbinil Retinopathy Trial Research Group: A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Arch Ophthalmol 108:1234-1244, 1990.

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Studies of the Ocular Complications of AIDS (SOCA)

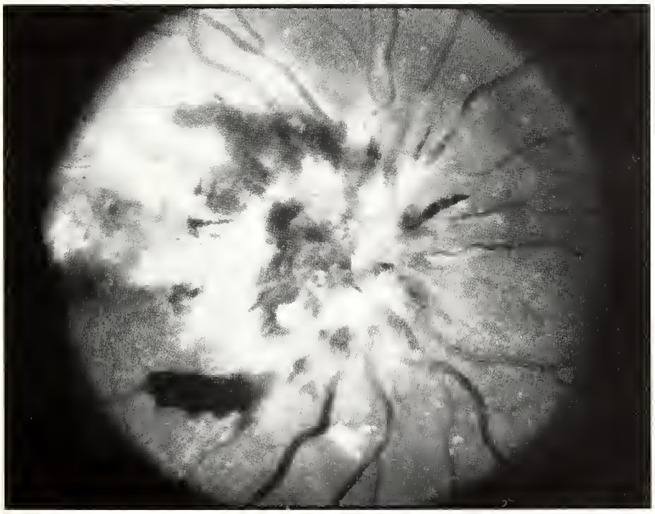
STUDY CHAIRMAN:	Douglas A. Jabs, M.D.
INSTITUTIONS:	11 Clinical Centers 4 Resource Centers

PURPOSE

To address issues related to eye involvement in patients with the acquired immune deficiency syndrome (AIDS), the National Eye Institute has funded the Studies of the Ocular Complications of AIDS (SOCA), a multicenter group to conduct clinical trials and epidemiologic studies. The first of these studies is the CMV Retinitis Trial (CRT). This randomized, controlled clinical trial is being sponsored jointly by SOCA and the AIDS Clinical Trials Group (ACTG). The ACTG is funded by the National Institute of Allergy and Infectious Diseases to conduct clinical trials relating to the treatment of patients with AIDS.

The purpose of the CMV Retinitis Trial (CRT) is:

- To evaluate the relative safety and efficacy of ganciclovir and foscarnet for the treatment of cytomegalovirus (CMV) retinitis, the most common intraocular infection in patients with AIDS.
- To determine the relative merits of immediate therapy versus deferral of therapy for the treatment of small peripheral lesions in patients with CMV retinitis.
- To evaluate the effects of treatment with ganciclovir or foscarnet on patient survival.



Courtesy of Douglas A. Jabs, M.D.

CMV retinitis in a patient with AIDS.

BACKGROUND

CMV retinitis is the most common intraocular infection in patients with AIDS, affecting an estimated 20-25 percent of patients. Untreated, CMV retinitis is a progressive and potentially blinding disorder. Given current projections for the AIDS epidemic, it is estimated that there may be as many as 20,000 new cases of CMV retinitis in 1992.

Two drugs now available for the treatment of CMV retinitis are ganciclovir and foscarnet. Ganciclovir, a nucleoside analog that inhibits viral replication, is the only drug approved by the Food and Drug Administration (FDA) for the treatment of CMV retinitis. Treatment of CMV retinitis is not curative; long-term suppressive therapy is required. Therefore, the drug, which is available only as an intravenous formulation, is given in a two-step fashion with an initial 2-week high dose (induction) treatment, followed by long-term lower-dose (maintenance) treatment.

Foscarnet is an investigational agent now being used for the treatment of CMV retinitis. Like ganciclovir, foscarnet is available only as an intravenous formulation, and it suppresses CMV retinitis. It is used in a similar two-step fashion with long-term maintenance required. Preliminary investigations suggest that ganciclovir and foscarnet are equally effective for the treatment of CMV retinitis. However, no comparative trial has been performed, and the toxicity profiles of the two drugs are quite different. Ganciclovir's primary toxicity is bone marrow suppression. Therefore, one generally does not treat patients with zidovudine (formerly known as azidothymidine or AZT) and ganciclovir concurrently. Conversely, foscarnet's toxicities are primarily renal and metabolic rather than hematologic; therefore, foscarnet can be used concurrently with zidovudine. Because zidovudine is used to treat HIV infection, there is the possibility of a differential effect on survival from the use of the two agents. However, given the degree of immunodeficiency present when patients develop CMV retinitis, zidovudine may of no further benefit at that time. This trial comparing the two agents for the treatment of CMV retinitis has been designed because of these issues.

Another issue relates to the management of small peripheral lesions in patients with CMV retinitis. Some investigators have favored immediate therapy in such cases with an anti-CMV agent. They hope immediate therapy will minimize the amount of retinal damage and reduce the risk of retinal detachment and visual loss. Other investigators believe that it is better to defer anti-CMV treatment until the retinitis becomes more immediately sight threatening, thereby allowing the patient to remain on zidovudine, and deferring the risks of central venous catheter infection and the potential toxicities of the anti-CMV drugs. Furthermore, some investigators believe that the risk of retinal detachment may be increased by the use of an anti-CMV agent. Such agents are known to inhibit the formation of retinal scars, which can act as anchors that prevent the retina from detaching. Other investigators feel the risk of retinal detachment is decreased by treatment, which minimizes the amount of retinal damage. To resolve these questions, a clinical trial comparing these two strategies for the treatment of peripheral lesions is needed.

DESCRIPTION

Approximately 240 patients will be enrolled in the CRT during the first 2 years of the study. Patients with zone 1 retinitis lesions, defined as less than 3,000 microns from the center of the macula or 1,500 microns from the optic nerve, will be randomized to therapy with either foscarnet or ganciclovir. Patients with retinitis in zone 1 (posterior pole) or extensive retinitis in zones 2 and 3 (peripheral retina) will receive immediate treatment with the randomly assigned drug.

Patients with retinitis that is confined to less than 25 percent of zones 2 and 3 will be offered the choice of either participating in a randomized comparison of immediate therapy or deferral of therapy or choosing one of these treatment options themselves. For patients choosing either of these options, only the drug treatment will be randomly assigned. Patients in the deferral groups will begin treatment when and if their retinitis becomes more sight threatening.

Because of the differences in drug administration methods, treatment will not be masked. However, evaluation will be conducted in a masked fashion by the Fundus Photograph Reading Center. Outcome measures of the clinical trial include survival, retinitis progression, changes in visual acuity or visual fields, drug toxicity, and presence of active CMV. Patients will be followed until death or common study closeout.

PATIENT ELIGIBILITY

Males and females eligible for the CRT must be age 13 or older and have AIDS (CDC definition) or laboratory confirmation of HIV infection and CMV retinitis. They cannot have received previous treatment with an anti-CMV drug for their CMV retinitis. Furthermore, they must have an absolute neutrophil count (ANC) greater than or equal to 1,000 cells/microliter and a serum creatinine less than or equal to 2.0 mg/dl in order to be able to tolerate either drug.

PATIENT RECRUITMENT STATUS

Ongoing. Recruitment began in March 1990.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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CORNEAL DISEASES PROGRAM

Clinical Trial of Eye Prophylaxis in the Newborn

STUDY CHAIRMAN: J. Thomas Grayston, M.D.
INSTITUTION: University of Washington

PURPOSE

- To compare the effectiveness of silver nitrate drops, erythromycin ointment, or no medication in preventing neonatal conjunctivitis caused by *Chlamydia trachomatis* and other eye infections.
- To compare side effects of prophylactic agents for the presentation of neonatal conjunctivitis.

BACKGROUND

Sexually transmitted diseases are a major cause of neonatal eye infections. All 50 states require some eye treatment at birth to prevent gonorrheal eye infections. Approximately 3 to 4 million Americans acquire a genital chlamydial infection each year, and more than 150,000 infants are born to mothers with chlamydial infections. These infants are at high risk of developing conjunctivitis and pneumonia.

In the State of Washington, one of three treatments is presently required by law to help prevent gonorrheal eye infection in newborn babies: 1 percent silver nitrate drops, erythromycin ointment, or tetracycline ointment. Although all three treatments appear to prevent eye infections from gonorrhea, silver nitrate and erythromycin may partially prevent chlamydial conjunctivitis. However, silver nitrate may irritate and damage the eyes of newborns. If it is not known whether the mother is infected, it may be better not to give the drugs routinely. It cannot be clearly established from the medical literature whether the risk to infants from no treatment is higher or lower than the risk from receiving a prophylactic agent. Many parents at low risk for gonorrhea prefer to have no prophylaxis given to their newborns. Moreover, Great Britain has used no eye prophylactic agents for newborns for 25 years and its rates of neonatal conjunctivitis are similar to those in the United States. For these reasons, the Washington State Board of Health has granted this study an exemption from the State law to allow the investigators to evaluate scientifically the risks and benefits of no treatment.

DESCRIPTION

The study is a randomized, double-masked clinical trial planned to include 1,200 infants born over 3 years. The trial will compare the efficacy of two treatment regimens, silver nitrate and erythromycin in two treatment groups, to a control group receiving no prophylaxis. (Erythromycin was chosen over tetracycline as the antibiotic in this study because it is more commonly used in the United States for ocular prophylaxis.) The infants are randomly assigned to one of these three groups in the delivery room. Infants without conjunctivitis are monitored for 2 months after delivery. Infants developing conjunctivitis are monitored for 2 months after successful treatment of their infection. The study includes extensive efforts to determine

Courtesy of Thomas Bell, M.D.

Instillation of fluorescein with impregnated paper strip.

Courtesy of Thomas Bell, M.D.

Observation of residual fluorescein with cobalt blue filtered light.

the etiology of the conjunctivitis and the presence of nasolacrimal duct obstruction.

The first 3 years of patient recruitment have been completed. None of the 450 women enrolled in the study to date has been found to have gonorrhea. The attack rate of conjunctivitis in the first 2 months of life for the entire cohort is approximately 18 percent.

PATIENT ELIGIBILITY

The study includes only male and female infants delivered at University Hospital in Seattle, Washington. Women are recruited after the 28th week of pregnancy and must be English speaking. In addition, they must be planning to stay at the hospital at least 48 hours following delivery and live in the greater Seattle metropolitan area. Infants delivered by vaginal or Caesarean births are eligible. Excluded from the study are siblings of infants enrolled in the study, women who are culture-positive for gonorrhea, infants receiving systemic antimicrobials for reasons other than conjunctivitis, women receiving antimicrobials at the time of delivery, and families unlikely to be available for followup after delivery.

The trial will continue to recruit patients until it has fulfilled the required sample size (1,200), unless the investigators note any undue health risk to the infants.

PATIENT RECRUITMENT

Ongoing. Recruitment began in August 1985.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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Collaborative Corneal Transplantation Studies (CCTS)

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INSTITUTIONS:
6 Clinical Centers
2 Resource Centers

PURPOSE

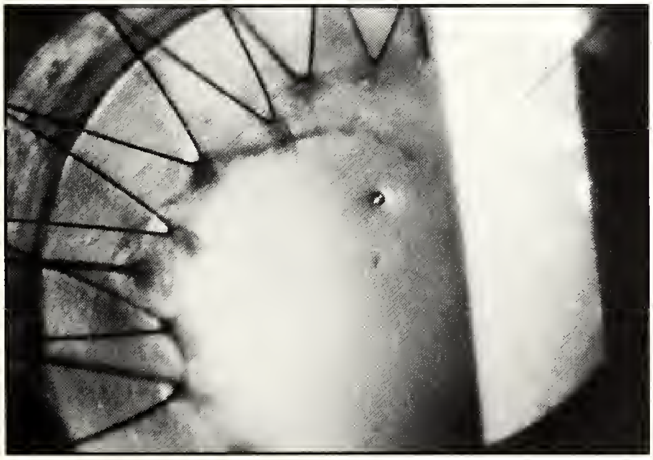
To determine whether histocompatibility matching of corneal transplant donors and recipients can reduce the incidence of graft rejection in high-risk patients.

BACKGROUND

Approximately 20 percent of corneal transplant patients, about 6,000 per year, face donor tissue rejection at rates of up to 60 percent because of corneal vascularization or prior graft rejection. Histocompatibility antigen matching and/or crossmatching may offer these patients an improved chance for successful outcome.

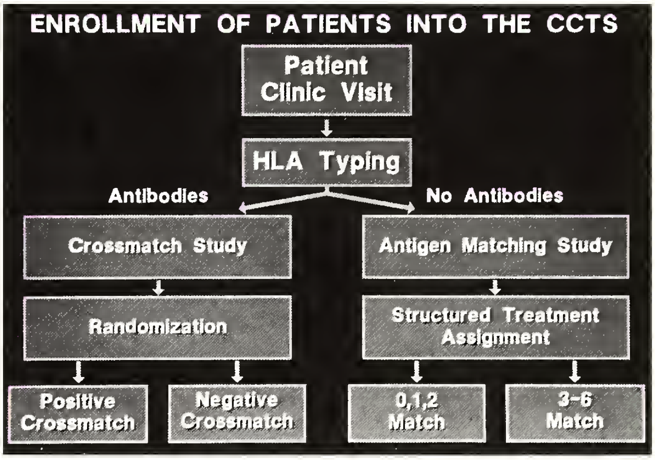
DESCRIPTION

The Collaborative Corneal Transplantation Studies Group is conducting two controlled, double-masked studies addressing distinct scientific questions about donor-recipient histocompatibility matching. **The Crossmatch Study** is a randomized study assessing the effectiveness of crossmatching in preventing graft rejection among high-risk patients with lymphocytotoxic antibodies. The **Antigen Matching Study** is a prospective, partially-randomized, observational study of the effectiveness of HLA-A, HLA-B, and HLA-DR donor-recipient matching in high-risk patients who have no lymphocytotoxic antibodies. Six clinical centers are recruiting high-risk patients and collaborating with their local eye banking and organ procurement agencies in procuring donor corneal tissue. For each of the two studies, a total of 400 patients is being sought. Blood samples from each enrolled patient are sent to the local CCTS tissue-typing laboratory for HLA typing, and serum samples are sent to the Central Laboratory for screening for preformed lymphocytotoxic antibodies. Depending on the results of the testing, patients are entered into either the Crossmatch Study or the Antigen Matching Study.



Courtesy of Walter J. Stark, M.D.

Endothelial rejection line in a pretransplant CCTS patient.



Courtesy of Walter J. Stark, M.D.

CCTS study protocol.

As corneal donors become available, donor blood samples are HLA-typed at the local laboratories and crossmatched against all CCTS patients awaiting transplantation. Results of the testing are entered in a national, 24-hour, computerized allocation system operated by the United Network for Organ Sharing (UNOS). Patients in the Crossmatch Study receive corneas from either positively crossmatched donors or negatively crossmatched donors. Patients in the Antigen Matching Study receive corneas with 0 to 6 matched antigens.

Transplant patients are followed intensively during the first months after surgery. Clinic visits are tapered to two during the third and final year of followup, resulting in a total of 17 postoperative visits. Irreversible failure of the corneal allograft due to rejection is the primary outcome variable in both studies. Allograft reaction episodes, irreversible failure due to all causes, and visual acuity are secondary outcome variables.

PATIENT ELIGIBILITY

Males and females ages 10 years or older with 2 to 4 quadrants of corneal stroma vascularization or a history of allograft rejection in the eye to be considered for surgery are eligible for both studies in the CCTS.

Patients must be willing to participate in 3 years of followup. No one who has a condition that would greatly increase the risk of non-rejection graft failure, such as xerophthalmia or severe exposure keratopathy, will be eligible for the CCTS. Also excluded are patients with either systemic diseases or medication usage that might alter their immune responses.

PATIENT RECRUITMENT

Recruitment began in May 1986 and was completed September 30, 1989.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

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Herpetic Eye Disease Study (HEDS)

STUDY CHAIRMAN: Chandler R. Dawson, M.D.
INSTITUTIONS: 8 Clinical Centers
1 Resource Center

PURPOSE

- To determine how two different antiviral agents and a topical corticosteroid affect the progression and severity of ocular herpetic disease.
- To provide an overview of the natural history of ocular herpes simplex virus infections under currently used treatment.
- To provide a framework for therapeutic trials of other infectious and inflammatory eye diseases.

BACKGROUND

Infection of the eye by herpes simplex virus (HSV) is a leading cause of corneal blindness in the United States and other countries. It can lead to corneal scarring and neovascularization, permanent endothelial dysfunction and corneal edema, secondary glaucoma, and cataract. Despite the availability of four antiviral agents highly active against HSV keratitis, there is still no effective method for reducing the frequency of recurrence or severity of stromal keratitis and iridocyclitis. In addition, the prognosis is poor for recovery of good vision following penetrating keratoplasty for actively inflamed or highly vascularized herpetic corneas.

DESCRIPTION

On the basis of both animal and human studies, the antiviral agent acyclovir appears to offer opportunities both for providing specific treatment and for preventing recurrence of HSV disease. However, no consensus yet exists on the management of herpetic eye disease to establish therapeutic guidelines for the use of other antivirals, such as trifluridine and anti-inflammatory agents.

There are three components of this study to examine the treatment of herpes simplex in stromal keratitis and iridocyclitis:

Herpes Stromal Keratitis, Not on Steroid Treatment (SKN). The SKN is a randomized, double-masked, controlled clinical trial of HSV stromal keratitis in patients not currently using a topical corticosteroid. Treatment with topical corticosteroid versus placebo is given in decreasing frequency for a 10-week period. All patients are treated with topical trifluridine, an antiviral agent. Successful outcome for the SKN study is resolution of the stromal opacity and inflammation to a stable state that does not change for 2 weeks after completion of the treatment regimen. The SKN recruitment goal is 178 patients.

Herpes Stromal Keratitis, on Steroid Treatment (SKS). The SKS is a randomized, double-masked, controlled clinical trial for patients with HSV stromal keratitis who are receiving a decreasing dosage of topical corticosteroid over a 10-week period. Treatment with oral acyclovir (ACV), or placebo capsules, is given for a 10-week period. Successful outcome for the SKS is the same as that for SKN, above. The SKS recruitment goal is 104 patients.

Herpes Simplex Virus Iridocyclitis, Receiving Topical Steroids (IRT). The IRT is a randomized, double-masked, controlled clinical trial studying HSV iridocyclitis in patients who also receive a progressively decreasing dosage of topical corticosteroid over 10 weeks. Treatment with oral ACV versus placebo is given for a 10-week period. Successful outcome for the IRT is resolution of iridocyclitis with fewer than 1+ cells in the anterior chamber and no significant keratitis and with stabilization for 2 weeks after completion of treatment. The IRT recruitment goal is 104 patients.

The examinations and technical procedures performed in all three studies include visual acuity, slit lamp biomicroscopy, tonometry, antibody tests for HSV, and clinical photomicrography. ACV is administered in 200-mg capsules (400 mg 5 times a day), and there are similar placebo capsules. Trifluridine and placebo drops are dispensed from identical bottles, and the corticosteroid preparation (prednisolone phosphate 0.12 percent and 1.0 percent) and placebo drops are likewise in identical bottles.

A change in visual function before and after treatment is a secondary outcome in these studies. Pretreatment visual acuity is expected to be compromised by the disease process. Because improvement in visual acuity associated with antiviral or corticosteroid treatment is expected, it is be measured.

PATIENT ELIGIBILITY

Male and female candidates for the study must be age 12 or older and have active herpes simplex stromal keratitis with or without iridocyclitis. Symptoms must not be caused by other focal stromal inflammation.

Patients are excluded if they have dendritic keratitis, geographic keratitis, significant epithelial defects that are greater than 1.0 mm in diameter, or previous keratoplasty of the involved eye. Women 15 to 50 years of age may be included if they are not pregnant, are using some form of birth control, and do not intend to become pregnant during the course of antiviral treatment.

PATIENT RECRUITMENT

Ongoing. Recruitment began in September 1988.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

Dawson CR: The Herpetic Eye Disease Study. Arch Ophthalmol 108:191-192, 1990.

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Prospective Evaluation of Radial Keratotomy (PERK)

STUDY CHAIRMAN: George O. Waring III, M.D.

INSTITUTIONS: 9 Clinical Centers
2 Resource Centers

perk
Prospective Evaluation
of Radial Keratotomy

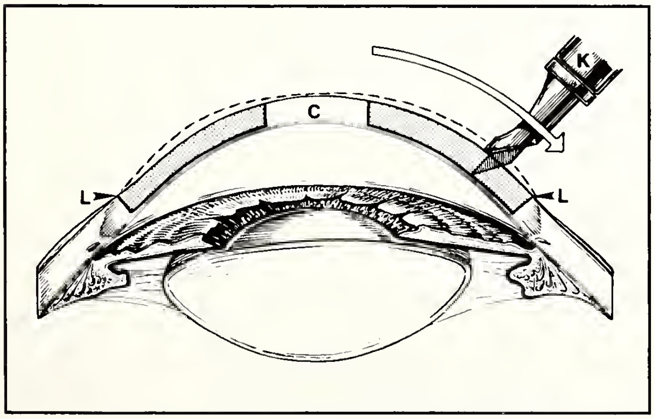
PURPOSE

- To determine whether radial keratotomy is effective in reducing myopia.
- To detect complications of the surgery.
- To discover patient characteristics and surgical factors affecting the results.
- To determine the long-term safety and efficacy of the procedure.

BACKGROUND

Approximately 11 million Americans have myopia that can be corrected with eyeglasses or contact lenses. Some of these people may also be candidates for radial keratotomy (RK), a procedure that aims to correct or reduce myopia by surgery that flattens the corneal curvature.

Keratotomy was first performed by surgeons in Europe and the United States in the late 1800's, and the basic optical and mechanical principles of the operation were defined in the 1940's and 1950's by the Japanese doctors, T. Sato and K. Akiyama, who used anterior and posterior corneal incisions. The posterior incisions damaged the cornea, and the procedure was modified in the Soviet Union by doctors S.N. Fyodorov and V. Durnev to include incisions in only the anterior cornea. Since its introduction in the United States in 1978, numerous ophthalmologists have made technical and surgical improvements in the procedure, such as ultrasonic methods to measure the thickness of the cornea and the use of diamond-bladed micrometer knives to make the incisions.



Courtesy of George O. Waring III, M.D.

PERK surgical technique: Blade length is 100 percent of the thinnest paracentral reading.

However, scientific assessment of RK lagged behind growing public and professional interest in the procedure. In 1980, in response to widespread concern about the long-term safety and efficacy of RK, a group of ophthalmic surgeons approached the National Eye Institute with a proposal for a multicenter clinical trial that would evaluate the potential benefits and risks of this procedure.

DESCRIPTION

The Prospective Evaluation of Radial Keratotomy (PERK) study, involving 435 patients, is a controlled clinical trial designed to evaluate the short- and long-term safety and efficacy of radial keratotomy. The procedure is evaluated by comparing a patient's vision before and after surgery. The more myopic eye received surgery first. For patients with a similar degree of myopia in both eyes, one eye was randomly selected for surgery. Patients were required to wait 1 year before having the operation on the second eye.

The surgical technique was standardized, consisting of eight radial incisions with a diamond micrometer knife. The diameter of the central, uncut, clear zone was determined by the preoperative spherical equivalent cycloplegic refraction (-2.00 to -3.12 D = 4.0 mm; -3.25 to -4.3 D = 3.5 mm; -4.50 to -8.00 D = 3.0 mm). The blade length was set at 100 percent of the thinnest of four intraoperative ultrasonic corneal thickness readings taken paracentrally at the 3, 6, 9, and 12 o'clock meridians just outside the trephine mark delineating the clear zone. The incisions were made from the edge of the trephine mark to the limbal vascular arcade and were equidistantly spaced around the cornea.

Patients were examined preoperatively and after surgery at 2 weeks, 3 months, 6 months, and annually for 5 years. Plans for long-term followup at 10, 15, and 20 years after surgery are being considered. Examinations in the morning and evening of the same day were done at 3 months, 1 year, and 3 years in a subset of the patients to test for fluctuating vision.

The primary outcome variables measured at each visit were the uncorrected and best-corrected visual acuity and the refractive error with the pupil dilated and undilated. The corneal shape was measured with central keratometry and photokeratoscopy. Endothelial function was evaluated using specular microscopy. A slit lamp examination was made to check for complications from the incisions. Possible glare complications were studied with contrast sensitivity testing. Patient motivation and satisfaction were studied with a psychometric questionnaire.

PATIENT ELIGIBILITY

All men and women had from 2 to 8 diopters of simple myopia and were correctable to 20/20 or better with glasses or contact lenses. All patients had the stability of their myopia documented by previous records. Patients were at least 21 years of age and lived in the metropolitan areas of the study centers. Each patient agreed to have surgery on one eye and to wait 1 year for surgery on the other eye. Patients with systemic diseases that might affect corneal wound healing and patients with high corneal astigmatism were excluded from the study.

PATIENT RECRUITMENT STATUS

Recruitment began in April 1981 and was completed in October 1983.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

In the PERK study, it was found that radial keratotomy reduced myopia, but that the effectiveness of the outcome varied among patients. Among 390 eyes (90 percent followup rate) at 4 years after surgery, myopia was reduced in all eyes except one. The refractive change ranged from a 0.62 diopter increase in myopia to a 9.75 diopter decrease in myopia and averaged 3.81 diopters (SD = 1.64). For 55 percent of the eyes, the refractive error was within 1 diopter of emmetropia, 28 percent of eyes were undercorrected, and 17 percent were overcorrected by more than 1 diopter. At 4 years after surgery, 52 percent of eyes saw 20/20 or better, 76 percent of eyes saw 20/40 or better, and 2 percent of eyes saw 20/200 or worse. The surgery was more effective for patients with preoperative refraction between -2 and -4.37 diopters.

Although refractive error and uncorrected visual acuity are the most common measures used to assess the effectiveness of refractive corneal surgery, in some cases these two measures give conflicting evidence. Therefore, a visual function score combining refractive error and uncorrected visual acuity was devised that classified patients into excellent, good, fair, and poor visual function outcomes. Patients in the excellent category had a refractive error of -1 to +0.50 diopter and uncorrected visual acuity of 20/25 or better. Patients in the poor category had a refractive error with more than 3 diopters of myopia or more than 2 diopters of hyperopia and an uncorrected visual acuity of 20/100 or worse. Patients in the good and fair categories had intermediate values of refractive error and visual acuity. For PERK patients 4 years after surgery, the values of the visual function score were excellent, 39 percent; good, 29 percent; fair, 20 percent; and poor, 12 percent.

The ability of a patient to function without spectacles or contact lenses after radial keratotomy is a partial indicator of the success of the surgery. Of 323 patients with operations on both eyes operated at 4 years, 208 (64 percent) stated that they wore no correction on either eye.

Serious complications were relatively rare. Nine eyes lost two or three lines of best corrected visual acuity, eight eyes experienced vascularization of the incisions, two eyes had delayed bacterial keratitis, and four eyes had recurrent epithelial erosions. Eleven percent of the eyes had an increase in refractive astigmatism of 1 diopter or more.

The primary factors affecting the surgical outcome were the age of the patient, the diameter of the clear zone, and the depth of the incision scar. An estimate of the variation in the refractive change among patients with the same age, clear zone, and depth of incision is ± 2.21 diopters.

The refractive error continues to change in some patients. Between 6 months and 4 years after surgery, 73 percent of eyes were relatively stable, with a refractive change less than 1 diopter. Four percent of eyes had an increase in minus power of 1 diopter or more. However, 23 percent of eyes had a decrease in minus power of 1 diopter or more, that is, a change in the direction of a continued effect of the surgery. Among unoperated control eyes, none had a decrease in myopia of 1 diopter or more during the 4-year followup.

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CATARACT PROGRAM

Randomized Trial of Aspirin and Cataracts in U.S. Physicians

STUDY CHAIRMAN: Charles H. Hennekens, M.D., Dr.P.H.

INSTITUTION: Brigham and Women's Hospital, Inc.
2 Resource Centers

PURPOSE

- To determine whether 325 mg of aspirin taken on alternate days reduces the risk of developing cataract among male U.S. physicians who were ages 40 to 84 in 1982.
- To identify potential risk factors for cataract development, such as age, blood pressure, blood cholesterol, height, diabetes, medication use, and history of previous eye trauma or surgery.

BACKGROUND

Cataract is one of the most common causes of impaired vision as well as the third leading cause of blindness in the United States. Although cataract surgery is one of the safest and most successful of all operations, the annual cost of this surgery in the United States is estimated at $1.35 billion. The National Eye Institute has estimated that if means were available to slow the progression of cataract enough to delay the need for surgery by even 10 years, the current annual number of nearly 1 million operations could be reduced by 45 percent, resulting in a savings of more than $607 million per year.

Little is known about the relative importance of various potential risk factors in the development of cataract. Most current information on risk factors has come from anecdotal reports or relatively small case-control studies. One major project, the Framingham Eye Study, has identified several factors that were significantly associated with subsequent cataract formation, including diabetes and dietary factors. Diabetes has long been thought to increase the risk of developing cataract.

DESCRIPTION

Recently, aspirin has been proposed as a drug to prevent cataract formation or slow its progression. Aspirin may affect tryptophan levels in patients with cataract or inhibit aldose reductase, an enzyme associated with the development of diabetic cataract. Data from this study will determine whether one 325 mg aspirin tablet, taken on alternate days, protects against cataract formation and whether additional cataract risk factors emerge after simultaneously controlling for other variables.

The other primary objective of this trial is to assess the antioxidant effects of beta-carotene (50 mg on alternate days) on cataract development. In addition, factors which have been suggested to be cataractogenic will also be assessed using nested case-control methods. These factors include age, blood pressure, blood cholesterol, height, diabetes, medication use, cigarette smoking, and history of previous eye trauma or surgery. In addition, the possible associations between history of vitamin E and selenium intake and cataract will be explored.

This trial is part of the Physicians' Health Study, an ongoing, randomized, placebo-controlled, clinical trial of aspirin in the prevention of cardiovascular mortality and beta-carotene in the prevention of cancer. Following randomization, each of the 22,071 physicians enrolled was assigned to one of four groups to take either aspirin or its placebo and beta-carotene or its placebo. Followup questionnaires are sent at 6 and 12 months after randomization and every 12 months thereafter. The average length of followup is now greater than 5 years.

Since this study is conducted by mail among physicians nationwide, examinations cannot be performed on all patients to determine when they have reached an end point. Reported diagnoses of cataract are confirmed by medical record review. The primary analysis will be incidence of cataract in the aspirin and placebo groups. In addition, the Cox proportional hazards model will be used to determine whether there is a difference in time to cataract diagnosis between the two groups. It has been postulated that the potent antioxidant properties of beta-carotene might make it effective in preventing cataract development. The investigators will thus determine whether there is a difference between the numbers of cataracts in the beta-carotene/placebo groups and the incidence of cataracts in those who are taking aspirin or its placebo.

PATIENT ELIGIBILITY

The study population consists of 22,071 male U.S. physicians, ages 40 to 84 years in 1982, with no history of myocardial infarction, cancer, kidney disease, renal disease, or any other contraindication to the use of aspirin or beta-carotene, including regular use of corticosteroids.

PATIENT RECRUITMENT

Recruitment began in April 1982 and was completed in December 1984.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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GLAUCOMA PROGRAM

Advanced Glaucoma Intervention Study (AGIS)

STUDY CO-CHAIRMEN: Douglas E. Gaasterland, M.D., and Fred Ederer, M.A., F.A.C.E.
INSTITUTIONS: 11 Clinical Centers
1 Resource Center

AGIS

PURPOSE

To assess the long-range outcomes of sequences of interventions involving trabeculectomy and argon laser trabeculoplasty in eyes that have failed initial medical treatment for glaucoma.

BACKGROUND

In advanced glaucoma, medication alone no longer reduces intraocular pressure adequately and the eye has field defects. Before 1980, some type of filtering surgery, such as trabeculectomy, had been the usual method of intervention. Since then, argon laser treatment has become a popular alternative as the initial treatment for advanced glaucoma. Sometimes the first intervention chosen succeeds in controlling pressure for many years; at other times, the success lasts only a few weeks or months. Because success is limited, some patients, over time, need to undergo a sequence of surgical interventions. Little is known about which sequence gives the best long-range outcome.

DESCRIPTION

The Advanced Glaucoma Intervention Study (AGIS) is designed to use two standard interventions for advanced glaucoma, trabeculectomy and argon laser trabeculoplasty (ALT), in differing sequences. Eligible eyes are randomly assigned to one of two intervention sequences: (1) trabeculectomy, followed by ALT should trabeculectomy fail, followed by a second trabeculectomy should ALT fail; or (2) ALT followed by trabeculectomy should ALT fail, followed by another trabeculectomy should the first trabeculectomy fail. Eyes that fail the assigned sequence of interventions will be managed by additional surgery. Interventions will be supplemented with medical treatment as needed.

A total of 840 eyes with advanced glaucoma will be enrolled over 3 years. All patients will be followed under a standardized protocol for a minimum of 5 years to determine degree of visual function loss, rates of failure of interventions and intervention sequences, rates of complications, and need for supplemental therapy.

After the initial intervention, followup examinations will be scheduled at 6 weeks, 3 months, 6 months, and every 6 months thereafter. In addition, after second, third, and subsequent interventions, followup examinations will be scheduled at 6 weeks and 3 months. Additional visits between study examination visits are scheduled for patients as necessary for the management of the disease.

Courtesy of Agis Coordinating Committee

IOP measurement. AGIS will clarify whether control of IOP preserves visual function.

PATIENT ELIGIBILITY

Men and women between the ages of 35 and 80 who have open-angle glaucoma that has not been successfully controlled by medication are eligible for enrollment in AGIS.

PATIENT RECRUITMENT

Ongoing. Recruitment began in April 1988. As of May 1990, 450 eyes of 338 patients had been enrolled.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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Fluorouracil Filtering Surgery Study (FFSS)

STUDY CHAIRMAN: Richard K. Parrish II, M.D.
INSTITUTIONS: 7 Clinical Centers
1 Resource Center

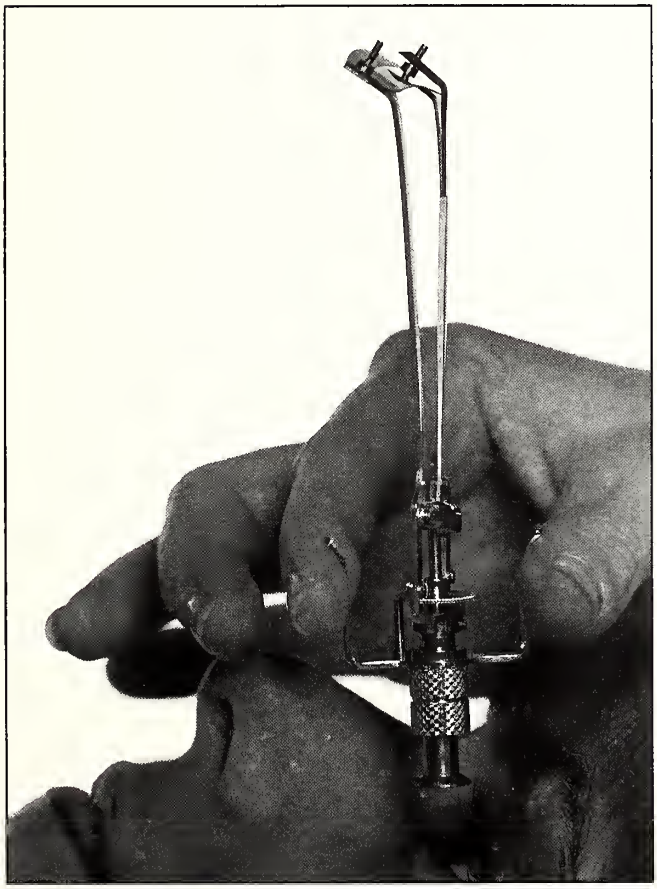
FLUOROURACIL
FILTERING
SURGERY
STUDY

PURPOSE

To determine if postoperative subconjunctival injections of 5-fluorouracil (5-FU) increase the success rate of filtering surgery in patients at high risk for failure after standard glaucoma filtering surgery.

BACKGROUND

Filtering surgery adequately lowers intraocular pressure in most glaucoma patients. However, the prognosis is less favorable for aphakic patients with glaucoma or glaucoma in phakic eyes following unsuccessful filtering operations. Failure of filtering surgery is usually attributed to the proliferation of fibroblasts at the filtering site. The use of 5-FU, an antimetabolite, has been shown to inhibit the proliferation of fibroblasts in tissue culture, and in preliminary studies it has increased the success of filtering surgery in a non-human primate model.



Courtesy of Fluorouracil Filtering Surgery Study (FFSS)

Flourouracil Filtering Surgery Study goal: intraocular pressure control.

DESCRIPTION

The Fluorouracil Filtering Surgery Study (FFSS) is a randomized, controlled clinical trial comparing the success rate of standard glaucoma filtering surgery to standard surgery with adjunctive 5-FU treatment. An ancillary study will provide data on the development of filtering blebs following surgery, both with and without use of 5-FU, and on the relationship of filtering bleb morphology and intraocular pressure control.

Another element of this study is to evaluate the frequency and severity of possible adverse effects related to 5-FU injections. Detailed preoperative and postoperative examinations of the cornea, lens, and retina will be done. Systemic toxicity will be assessed by preoperative and postoperative hematologic studies.

After the investigators perform the filtering surgery and determine that the new outlet channel is working, patients are randomized to receive either 5-FU injections or standard postsurgical care without 5-FU. The 5-FU-treated patients receive subconjunctival injections of 5 mg of 5-FU twice daily on postoperative days 1 through 7, and once daily on postoperative days 8 through 14. There have been 213 patients recruited into the study—162 with previous cataract extraction and 51 with previous filtering surgery.

All patients are examined at 1 month, 3 months, 6 months, and at 6-month intervals thereafter. Success and failure rates are calculated on the basis of the following intraocular pressure levels: Success (unqualified) is intraocular pressure (IOP), ≤ 21 mm Hg without ocular hypotensive medication, success (qualified) is IOP ≤ 21 mm Hg with ocular hypotensive medication, and failure is IOP > 21 mm Hg despite maximal ocular hypotensive medication 1 year postoperative, or IOP > 21 mm Hg despite maximal ocular hypotensive medication at the time of reoperation if reoperation occurs less than 1 year after initial surgery. Possible concomitant risks of 5-FU treatment, such as toxic effects to the cornea, lens, or retina, will be monitored.

PATIENT ELIGIBILITY

Men and women with uncontrolled intraocular pressure greater than 21 mm Hg in one or both eyes, despite maximal tolerated therapy, who are either aphakic or who have had previous filtering surgery, are eligible to participate.

PATIENT RECRUITMENT STATEMENT

Recruitment began in September 1985 and was completed in June 1988. The 213 patients enrolled in the study are being followed for 5 years postoperative.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

Results from the FFSS were announced in December 1989. One-year followup data demonstrated a 50 percent improvement in surgical control of glaucoma using 5-FU in patients at high risk for blindness. Of the 105 operations on eyes treated with 5-FU, 73 percent were successful at 1 year, compared with 50 percent of the 108 eyes in the standard therapy group.

Filtering surgery followed by postoperative injections of 5-FU provided an additional benefit. Two-thirds of the patients receiving treatment with 5-FU did not need to resume taking medications to control their glaucoma. In the standard therapy group, only about one-third maintained satisfactory pressure control without medication. Moreover, of those requiring medication after surgery, patients in the 5-FU group needed fewer types and lower doses of medications than those in the standard treatment group.

The 5-FU injections given twice daily for the first week and daily the second week sometimes caused corneal epithelial toxicity with epithelial defects, bacterial corneal ulcer, and anterior stromal scarring; however, these side effects were usually short-lived, and the patients tolerated them without substantial problems.

PUBLICATIONS

The Fluorouracil Filtering Study Group: Fluorouracil Filtering Surgery Study one year followup. Am J Ophthalmol 108:625-635, 1989.

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Glaucoma Laser Trial (GLT)

STUDY CHAIRMAN: Hugh Beckman, M.D.

INSTITUTIONS:
8 Clinical Centers
3 Resource Centers

PURPOSE

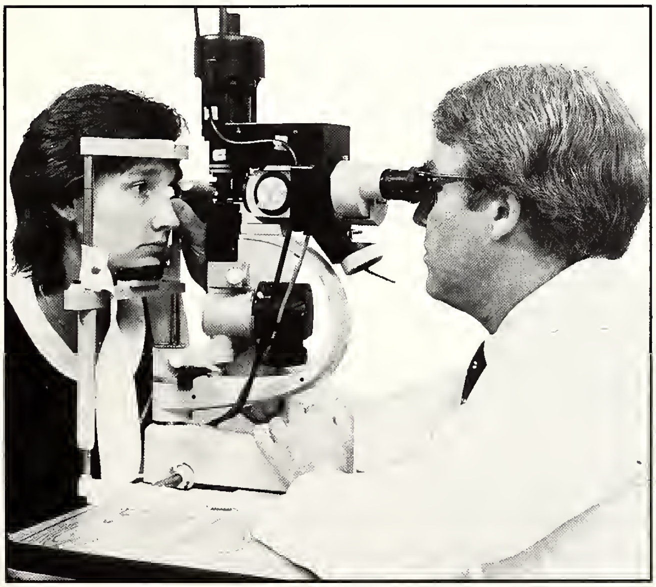
To compare the safety and long-term efficacy of argon laser treatment of the trabecular meshwork with standard medical treatment for primary open-angle glaucoma.

BACKGROUND

During the last decade, argon laser trabeculoplasty (ALT) has often been used instead of surgery as the treatment of choice in cases of open-angle glaucoma that could not be controlled by drugs. ALT treatment consists of tiny laser burns evenly spaced around the trabecular meshwork. It sometimes has been found to be effective in controlling glaucoma, although many eyes still require some medical treatment.

DESCRIPTION

The Glaucoma Laser Trial (GLT), a randomized, controlled clinical trial, is being conducted to find out whether ALT is effective in patients with newly diagnosed, primary open-angle glaucoma. Each of the 271 patients in the trial receives argon laser treatment in one eye and standard topical medication in the other eye. The eye to be started on medicine and the eye that will get the laser treatment are randomly selected.



Courtesy of GLT Coordinating Center

Patient seated at the laser.

The argon laser treatment is done in two sessions 1 month apart. One-half of the trabecular meshwork is treated with 45 to 55 laser burns in each session. Patients are seen for a followup visit 3 months after the first laser treatment and every 3 months thereafter for a period of at least 2 years. At each visit, examination of the eyes includes a check of intraocular pressure and visual acuity. Visual field examinations are performed 3, 6, and 12 months after randomization and annually thereafter. Disc stereophotographs are taken 6 and 12 months after randomization, and annually thereafter.

The results of these examinations determine whether treatment should be changed. If the pressure in either eye has not been reduced to the desired level, the physician changes the medication in the eye treated with drops, according to a standardized procedure being used in the trial, or starts the use of drops in the laser-treated eye. If intraocular pressure is still not successfully reduced, surgery or further laser treatment may be required.

PATIENT ELIGIBILITY

At the time of recruitment, men and women had to be at least 35 years old with an intraocular pressure of at least 22 mm Hg in each eye and evidence of optic nerve damage in at least one eye.

PATIENT RECRUITMENT

Completed. Recruitment was conducted between January 1984 and April 1987.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING PROGRAM

Optic Neuritis Treatment Trial (ONTT)

STUDY CHAIRMAN: Roy W. Beck, M.D.
INSTITUTIONS: 16 Clinical Centers
2 Resource Centers

PURPOSE

- To establish guidelines for deciding treatment for patients with optic neuritis.
- To determine whether treatment with corticosteroids reduces the residual optic nerve damage produced by optic neuritis.
- To determine whether corticosteroids speed the recovery of patients with optic neuritis.

BACKGROUND

Optic neuritis is second only to glaucoma as the most common acquired optic nerve disorder in persons under age 50, especially for individuals between the ages of 15 and 45. In this disorder closely linked to multiple sclerosis, the prognosis for visual recovery is generally good. However, the return of visual function is almost never complete.

After resolution of optic neuritis, virtually all patients show some signs of optic nerve damage; most are symptomatic. Approximately 25 percent of patients are left with reduced visual acuity and about 14 percent are within the legally blind range (20/200 or worse). However, even when a patient's acuity does recover to 20/20, abnormalities frequently remain in other measures, such as contrast sensitivity, color vision, and visual field.

Well-established guidelines for treating optic neuritis do not exist. Although corticosteroids have been used to treat this disease, studies to demonstrate their effectiveness have not been satisfactory. Furthermore, corticosteroids have potential side effects for which patients should not be put at risk if the treatment is ineffective. Thus, it is appropriate and necessary to test whether corticosteroid treatment safely and effectively reduces residual optic nerve damage produced by optic neuritis.

DESCRIPTION

The Optic Neuritis Treatment Trial (ONTT) is a multicenter, randomized, controlled clinical trial designed to determine whether corticosteroids will speed recovery and decrease residual visual dysfunction after resolution of optic neuritis. The trial will enroll approximately 435 patients at 16 clinical centers, with each center entering approximately 10 patients each year. Patient recruitment will last 3 years. All study participants will be followed periodically during the first 6 months, with followup yearly for the duration of the 4-year study.

Patients are randomized to one of three treatment regimens: (1) oral prednisone for 14 days; (2) intravenous methylprednisolone for 3 days, followed by oral prednisone for 11 days; (3) oral placebo for 14 days. The oral prednisone and placebo group will be double-masked; the intravenous methylprednisolone group will be single-masked.

In conjunction with the randomized treatments, additional tests are performed on accepted patients before treatment begins. In regular followup visits, the patient's progress is assessed by using contrast sensitivity, perimetry, visual acuity, and color vision tests. At the 6-month visit, the major outcome is determined. After that, all patients will be followed at yearly intervals until the end of the ONTT.

PATIENT ELIGIBILITY

The ONTT is accepting men and women between the ages of 18 and 45 who have acute unilateral optic neuritis with visual symptoms lasting 8 days or less and with no past episode of optic neuritis in the involved eye. Patients also must have a relative afferent pupillary defect and a visual field defect and may have a normal or swollen (but not pale) optic disc.

PATIENT RECRUITMENT

Ongoing. Recruitment began in July 1988.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

None.

PUBLICATIONS

None.

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The Prism Adaptation Study (PAS)

STUDY CHAIRMAN:	William E. Scott, M.D.
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PURPOSE

- To determine whether the preoperative use of prisms in eyeglasses can improve the outcome of surgery for acquired esotropia.
- To determine whether patients who respond to prism adaptation by developing a new stable angle of deviation have a better surgical result than patients who do not respond to prism adaptation.
- To determine whether those patients who respond to prism adaptation are more accurately corrected by operating for the prism-adapted angle or the original angle of deviation.
- To determine the usefulness of certain input variables (e.g., age at the time of surgery, size of the deviation, visual acuity, binocular function, refractive error) in predicting which patients are more likely to benefit from prism adaptation.

BACKGROUND

Acquired esotropia (crossed eyes that develop after a child reaches age 6 months) accounts for 25 percent of all patients with misaligned eyes. Surgery to correct esotropia is done primarily to attain functional use of the two eyes together and secondarily for cosmetic reasons. In 40 to 50 percent of cases, more than one operation is needed to accomplish this goal, and in some cases even three and four operations are needed.

Courtesy of Henry Metz, M.D.

Prism adaptation patient with prisms attached to glasses.

Preliminary studies done at two eye care centers reported that the use of prisms on eyeglasses for about a month before surgery led to good results after a single operation in over 90 percent of patients. These preliminary studies, done in a noncontrolled fashion, pointed to the need for a multicenter, randomized, controlled clinical trial designed to prove or disprove scientifically the beneficial effect of prisms.

DESCRIPTION

The Prism Adaptation Study is a double randomization trial involving 286 patients. Three-fifths of the patients are randomly selected for prism adaptation prior to surgery. Of those patients who respond to the prisms, one-half are randomly selected to have surgery on the basis of the amount of prism required to stabilize the deviation; the other half have surgery on the basis of amount of esotropia originally measured. Whether those patients who do not respond to the prisms also have surgery is based on the amount of esotropia measured as is surgery for the remaining two-fifths of the patients who do not undergo prism adaptation.

Patients are examined postoperatively at 1 week, 1 month, 3 months, 6 months, and 1 year. At the 6-month followup, an independent examiner evaluates the patient. The results are analyzed to determine whether the outcome is better in patients who underwent prism adaptation or those who underwent conventional treatment. Because the examiner does not know what type of treatment a patient has had, he or she has no bias in evaluating the results.

PATIENT ELIGIBILITY

To be eligible for this study, males or females must be age 3 years or older (adults may be included), must have esotropia that occurred at age 6 months or older, and must have no history of previous eye muscle surgery.

PATIENT RECRUITMENT

Recruitment began in March 1984 and ended in May 1989.

CURRENT STATUS OF STUDY

Ongoing.

RESULTS

Six months after surgery, there was a beneficial overall effect of the prism adaptation process for patients with acquired esotropia who met the study's "rather stringent" eligibility requirements. Success rates were highest (54 [89%] of 61 patients) in prism adaptation responders who underwent augmented surgery and lowest (92 [72%] of 127 patients) in patients who did not undergo prism adaptation at all. Prism responders who received augmented surgery also had better results than responders who underwent conventional surgery (89% vs. 79%). The results indicated a significant beneficial overall effect of prism adaptation in patients with acquired esotropia (success rates, 83% vs. 72%, P = .04), even when those who did not ultimately respond to the prisms were included. The investigators recommend that prism adaptation be considered for patients with acquired esotropia to determine the appropriate target angle for surgery.

PUBLICATIONS

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